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EXPERIMENTAL STREPTOCOCCIC INFLAMMATION IN NORMAL, IMMUNE AND HYPER- SENSITIVE ANIMALS*

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MINNEAPOLIS

In experimental work previously reported,¹ it was shown that inflammation with a cellular reaction similar to that found in tissues in cases of human rheumatic infection could be produced by the injection of streptococci of low virulence in small doses into the myocardium and the subcutaneous tissue of rabbits. With larger doses, abscesses developed. In these experiments, it was not determined whether the type of reaction was influenced by existing immune or allergic reactions, since most of the animals had had injections of streptococci before.

The experiments reported in this paper were carried on in an attempt to determine what part, if any, allergy or immunity played in the pathogenesis of these experimental lesions.

The phenomenon of allergy as related to inflammation, came into recent prominence with the work of Swift and his associates² by the discovery of the secondary reaction produced in rabbits following the intracutaneous injection of streptococci isolated from subcutaneous nodules in cases of acute rheumatic fever. These workers decided that

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* From the Department of Pathology, University of Minnesota.

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1. Clawson, B. J.: Experimental Rheumatoid Myocarditis, *Arch. Path.* **2**:799 (Dec.) 1926; Experimental Subcutaneous Rheumatic Nodules, *Am. J. Path.* **4**:565, 1928.

2. Andrewes, C. H.; Derick, C. L., and Swift, H. F.: The Skin Response of Rabbits to Non-Hemolytic Streptococci, *J. Exper. Med.* **44**:35, 1926. Derick, C. L., and Andrewes, C. H.: The Skin Response of Rabbits to Non-Hemolytic Streptococci, *ibid.* **44**:55, 1926. Derick, C. L., and Swift, H. F.: Hyperergic Tissue Response to Non-Hemolytic Streptococci, *Proc. Soc. Exper. Biol. & Med.* **25**:222, 1927; Immune Tissue Response to Non-Hemolytic Streptococci, *ibid.* **25**:224, 1927. Swift, H. F.; Hitchcock, C. H., and Derick, C. L.: General Tuberculin-Like Reactions in Rheumatic Fever Patients, Following Intravenous Injections of Streptococcus Vaccines of Nucleoproteins, *ibid.* **25**:312, 1928; Bacterial Allergy (Hyperergy) to Non-Hemolytic Streptococci, *J. A. M. A.* **90**:906 (March 24) 1928. Derick, C. L., and Swift, H. F.: Reactions of Rabbits to Non-Hemolytic Streptococci, *J. Exper. Med.* **49**:615, 1929.

this secondary reaction was an allergic phenomenon of the nature of the reaction of the skin to tuberculin rather than the Arthus phenomenon. The rabbits giving the secondary reaction were considered to be hypersensitive to streptococcic protein. This hypersensitiveness was called the hyperergic state. It was found that hypersensitiveness or bacterial allergy seemed to accompany the production of focal lesions of a certain intensity, and that it was probable that in these foci the substances or conditions were produced that led to bacterial allergy. This hypersensitiveness to streptococci was produced and maintained by the injection of agar and streptococci subcutaneously into the rabbits. It was also shown that this type of bacterial hypersensitiveness did not follow primary intravenous inoculations of rabbits with comparable doses of streptococci. The hypersensitive state was manifested by ophthalmic, skin and lethal reactions that were produced by the injection of streptococci into allergic animals in doses small enough to have no effect on nonsensitized animals. By tests with streptococcic vaccines, many patients with acute rheumatic fever were found to be hypersensitive to streptococcic protein. This was also confirmed with skin tests on patients with rheumatic fever by Birkhaug.³ These experiments and observations are of interest because they suggest that the clinical condition called acute rheumatic fever is definitely associated with and possibly dependent on a hypersensitiveness of the patient to streptococcic protein.

Allergic inflammation has come to be considered by many as a specific anatomic type of reaction and is thought of as being synonymous with proliferative or polyblastic inflammation. Swift stated that the anatomic features of tuberculous and syphilitic inflammations had been thoroughly established as allergic in their pathogenesis. Maximow,⁴ in speaking of allergic inflammation, said: "As far as one can judge by the still modest accumulation of facts available at present, the differences, as compared with the histogenesis of common inflammation, are quantitative rather than qualitative." Rich and McCordock⁵ offered objections to the idea that inflammation in persons or animals sensitized to tuberculo-protein had a specific characteristic. They were convinced that the inflammation occurring in the allergic state in association with tuberculosis showed a quantitative rather than a qualitative difference,

3. Birkhaug, K. E.: Rheumatic Fever; Allergic Reactions with Toxin-Producing Strain of Nonmethemoglobin-Forming Streptococcus Isolated from Rheumatic Fever, *J. Infect. Dis.* **43**:280, 1928; Rheumatic Fever; Skin Hypersensitiveness of Patients with Rheumatic Fever and Chronic Arthritides to Filtrates, Autolysates, and Bacterial Suspensions of Streptococci, *ibid.* **44**:363, 1929.

4. Maximow, A. A.: Morphology of the Mesenchymal Reactions, *Arch. Path.* **4**:557 (Oct.) 1927.

5. Rich, A. R., and McCordock, A. H.: The Pathogenesis of Human Tuberculosis, *Bull. Johns Hopkins Hosp.* **44**:273, 1929.

and that the anatomic type of reaction observed depended on the virulence, the number of organisms and the tissues into which the organisms were injected.

The term allergy in this paper is used to mean a state of hypersensitivity to a bacterial protein. There is no attempt to explain the relation between allergy and immunity or resistance; but a study is made of the relationship of experimental foci of inflammation, streptococcic in origin, to hypersensitiveness and to a general immune state as indicated by agglutinins in the blood. The following experiments were performed in an attempt to learn whether the experimental inflammation in hypersensitive or immune animals was different from the inflammation in normal animals. If it is proved that animals hypersensitive to a bacterial protein respond to doses too small to call forth any reaction in nonsensitive animals and react with the same type of cellular reaction which is produced by larger doses in nonsensitive animals, this fact may help to explain why, in rheumatic patients who have been found to be hypersensitive to streptococci, such extreme reactions take place when obviously few organisms are present in the blood, joints, heart, etc.

EXPERIMENTS

The experimental lesions to be reported were produced by injecting streptococci in many places into the subcutaneous tissues of rabbits. The organism used was a strain isolated before death from the blood of a patient having acute rheumatic fever. This strain had been kept on blood agar medium with frequent transfers over a period of eight years. The amount of sediment of organisms which would settle at the bottom of a test tube of a broth culture at forty-eight hours' incubation at 37 C. was used as a unit. The broth was poured off, and the sediment was made up with physiologic solution of sodium chloride to 10 cc. One-tenth cubic centimeter of the suspension or $\frac{1}{100}$ of the sediment (the larger dose) was injected into each of ten places in the subcutaneous tissues in the back of each animal on the right side, and $\frac{1}{1000}$ of the suspension (the smaller dose) was injected in a similar manner on the left side. By a series of previous experiments with increasing amounts, the dose of $\frac{1}{100}$ of the sediment was found to be the minimum amount which would produce subcutaneous nodules in normal animals with any degree of frequency, and it was found that with the dose of $\frac{1}{1000}$ of the sediment nodules were seldom produced. The animals were killed five days after the multiple injections were made. From previous experiments, it had been found that five days after the multiple injections was the optimum time for the development of subcutaneous nodules. The nodules, if present, were studied by gross and microscopic examination.

The experiments were performed with the following three groups of animals: (1) animals that had not had injections (normal animals);

(2) animals into which streptococci had been injected intravenously (immune animals); (3) animals into which in one area agar at 45 C., heavily seeded with streptococci, had been injected subcutaneously (allergic or hypersensitive animals). By this last method, Swift found it possible to keep his animals in the hypersensitive state. Before injections were made into any of the animals, blood was taken from the heart and tested for agglutinins in dilutions of 1:50 and upward. Agglutinins were detected in none.

Normal Animals (Group 1).—In these experiments, the animals of the first group were used as controls. After the blood of a normal animal had been tested for agglutinins and found to be negative, injections were made into the subcutaneous tissues of the back in many places with the larger dose in the right side and the smaller dose in the left side, as described. Five days later, the rabbits were killed,

TABLE 1.—Results of Subcutaneous Injection of Streptococci into Normal Animals

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1	3 small	0	0	200
2	1 small	0	0	200
3	2 small	0	0	200
4	1 small	0	0	200
5	2 small	0	0	0
6	3 small	3 very small	0	0
7	2 medium	0	0	0
8	0	0	0	200
9	0	0	0	0
10	0	0	0	0

and the nodules were examined. The blood was tested again for agglutinins. The experiments of this group are explained in table 1.

It is observed, by referring to table 1, that the inflammatory reaction in these ten normal animals was slight. At least ten injections were made on each side. Nodules were present with the larger doses in seven of the ten animals, but the number of nodules compared with the number of injections was small. All of these nodules were small, except in one case in which the two nodules were of medium size. In only one of the ten animals were there any nodules on the side into which the smaller dose had been injected. These nodules were very small.

By microscopic examination, the reaction in the smaller nodules was seen to be polyblastic. There were regular and irregular mononuclear and multinucleated cells, plasma cells, eosinophils, lymphocytes and a few polymorphonuclear leukocytes. In the centers of the few larger nodules, abscess formation was present, but a considerable degree of polyblastic reaction was always present in the periphery of these nodules.

Agglutinins were not present in any of the animals in this group at the time of the multiple injections. Five days after the multiple injections, five of the ten rabbits showed agglutinins in dilutions as high as 1:200. A titer of 1:200 is low when compared with the titer in the animals into which streptococci had been injected intravenously before the multiple injections. There was no apparent relation between the presence of these agglutinins and the number, size or character of the nodules in the normal animals.

TABLE 2.—Results of Subcutaneous Injection of Streptococci into Immune Animals

Rabbit	Number of Days Between Initial Dose and Multiple Injections	Nodules on Right Side	Nodules on Left Side	Agglutination	
				At Time of Multiple Injections	When Animals Were Killed
A	1	1 small	0	0	400
	2	1 small	0	0	400
	3	0	0	0	400
	4	0	0	0	400
	5	0	0	100	6,400
	6	0	0	100	6,400
	7	0	0	100	6,400
	8	0	0	100	6,400
	9	0	0	200	6,400
	10	0	0	200	6,400
	11	0	0	200	6,400
	12	2 small, firm	0	200	6,400
B	1	0	0	6,400	6,400
	2	4 medium	2 small	6,400	6,400
	3	6 medium	0	6,400	6,400
	4	2 medium	0	6,400	6,400
	5	3 medium	0	6,400	6,400
	6	3 small	0	6,400	6,400
	7	6 large	5 small	6,400	6,400
	8	5 medium	0	6,400	6,400
	9	5 medium	4 small, firm	6,400	6,400
	10	6 medium	3 small, firm	6,400	6,400
	11	8 medium	3 small, firm	6,400	6,400

Immune Animals (Group 2).—The second group consisted of thirty-one animals in which immunity, indicated by the presence of agglutinins, had been produced by an intravenous injection of streptococci. Multiple injections with $\frac{1}{100}$ and $\frac{1}{1000}$ of the sediment of a broth tube, as in group 1, were made subcutaneously into the tissues of the backs of the different animals at intervals of one, two, three, four, five, six, seven, eight, ten and twelve days (table 2). Eight other animals were highly immunized by being given four intravenous injections at intervals of five days. Seven days after the last intravenous injection, the multiple subcutaneous injections were given (table 3). The purpose of the experiments with the immune animals was to determine whether the progress of the cellular reaction at the points of the secondary multiple subcutaneous injections was increased as a result of a hypersensitive

condition occurring early in the development of a general immunity, as suggested by Zinsser;⁶ whether the reaction was retarded from acquired resistance; or whether a hypersensitive state developed near the twelve-day period following the primary intravenous immunizing dose. The results of these experiments are given in tables 2 and 3.

By table 2 it is seen that little reaction occurred, as indicated by the frequency, size and character of the subcutaneous nodules in the animals in the first half of the experiment or in the twelve animals which had received the multiple subcutaneous injections in from one to five days after the primary intravenous immunizing dose (table 2A). Nodules were present in three of these twelve animals. Only 4 nodules were seen of a possible 240. These four nodules were all on the right side, into which the larger doses were injected. The nodules were small

TABLE 3.—Results of Subcutaneous Injection of Streptococci into Hyperimmune* Animals

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1.....	1 small	0	64,000+	64,000+
2.....	2 small, firm	2 small, firm	64,000+	64,000+
3.....	0	0	64,000+	64,000+
4.....	0	0	256,000	300,000
5.....	0	0	256,000	300,000
6.....	2 small, firm	0	256,000	300,000
7.....	2 small, firm	0	256,000	300,000
8.....	0	0	256,000	300,000

* Animals were rendered hyperimmune by four intravenous injections of streptococci at intervals of five days.

and firm, and by gross examination did not appear to be abscesses. It was evident that these twelve rabbits showed no degree of hypersensitivity, and there was a suggestion that they had some degree of resistance, since the number and the size of the nodules were less than those found in normal animals.

Marked reaction took place in the eleven animals in the second half of group 2, the immune animals that had had the multiple subcutaneous injections in from six to twelve days after the primary intravenous inoculation (table 2B). The nodules were more frequent, were larger and sometimes occurred on the side into which the smaller doses were injected. In all of these eleven animals, except one, nodules were produced from the larger injections and in five from the smaller injections. They ranged in number from two to eight on the right side and from three to five on the left side. Into each side ten injections had been made.

6. Zinsser, H., and Yu, H.: Bacteriology of Rheumatic Fever and Allergy Hypothesis, Arch. Int. Med. 42:301 (Aug.) 1928.

The microscopic reaction differed in no way qualitatively from that found in the normal animals. No peculiarity in the reaction was observed.

Two factors may be thought of as the cause of this difference in the quantitative reaction in the two divisions in group 2: (1) the interval of time between the multiple subcutaneous injections and the primary immunizing inoculation, and (2) the degree of concentration of the immune bodies in the blood of the animals. It will be observed that in the twelve animals with little reaction (table 2A) the interval of time between the immunizing dose and the multiple subcutaneous injections was from one to five days, while in the eleven animals with the marked reaction (table 2B) the interval was from six to twelve days. The increased reaction in the second division might have been due to some degree of allergy, since allergic reactions are likely to occur in from six to fifteen days after an initial injection. It may be noticed that the degree of concentration of antibodies in the blood of the animals with little reaction was relatively low. It was never above 1:200 at the time of the multiple subcutaneous injections, and in four of the twelve animals no agglutinins were present at this time. The agglutinins at the time when the animals were killed, however, were high, 1:6,400+, in all, except in those in which the subcutaneous injections were made one day after the initial dose. In all the animals with marked subcutaneous nodules, the agglutinating titer was high, 1:6,400+, both at the time of the multiple subcutaneous injections and when the animals were killed.

Experiments were performed with the highly immunized animals in an attempt to determine whether the high antibody content of the serum rather than a hypersensitiveness was responsible for the greater frequency and larger size of the nodules. Only four of the eight animals highly immunized showed subcutaneous nodules (table 3). There was but one small nodule in the first animal, and this nodule was on the side into which the larger dose was injected. The second animal had two of a possible twenty nodules on each side. These four nodules were small and rather firm. The third, fourth, fifth and eighth animals had no nodules. The sixth and seventh animals each had two small firm nodules on the side into which the larger dose had been injected. In the eight animals there were 9 nodules of a possible 160. The microscopic structure of these nodules in the hyperimmunized animals was similar to that found in the small nodules in all the other groups.

It is to be observed that the agglutinating titer was high, 1:64,000 and 1:300,000. The experiments with these highly immunized animals suggested that the frequency and the size of the subcutaneous nodules were not increased by a high antibody content and that, when there was an increase in the number and size of the subcutaneous nodules

in animals which previously had had intravenous injections, this increase was due to a hypersensitive, or allergic, reaction, reaching its maximum intensity in from ten to twelve days after the primary intravenous injections, as it did in animals made hypersensitive from agar and streptococci.

Hypersensitive Animals (Group 3).—Five cubic centimeters of melted agar at 45 C., heavily seeded with streptococci, was injected subcutaneously into one area in each of the twelve animals of the third group. An abscess regularly developed at the point of inoculation. In from twelve to fifteen days, multiple subcutaneous injections were made into the back and sides of each animal with the larger and smaller doses of streptococci, $\frac{1}{100}$ of the sediment of a broth tube in each injection on the right and $\frac{1}{1000}$ on the left, as in groups 1 and 2. An interval of from twelve to fifteen days between the local injection and the secondary multiple injections was found by previous experiments to be the optimum for producing the best subcutaneous nodules.

The purpose of this experiment was to see whether the reaction following the secondary multiple subcutaneous injections was different, when a localized lesion was present, from the reaction occurring in the multiple subcutaneous nodules in normal animals and in animals immunized by intravenous injection. Swift showed by skin reactions that the allergic state depending on the localized lesion differed from the immune state which was produced by intravenous injection. This idea was held by Zinsser ⁷ and was expressed by Baldwin ⁸ and Krause ⁹ relative to the skin test in its relation to tuberculosis. The results of the experiments with the third group of animals are explained in table 4.

The gross reaction was pronounced in this group of animals. With the larger dose all of the twelve, except one, showed subcutaneous nodules and, with the smaller dose, nodules were present in all but three. With both doses, it should be observed that, as a rule, there were numerous nodules, many of which were large (fig. 1). The larger nodules were generally abscesses, and frequently there was a large red zone of injection about the area of abscess. It was obvious that the reaction in this group was definitely more extensive than in the other two groups. The production of nodules was evidently stimulated, in the hypersensitive animals, by smaller doses than in the normal or the immune animals.

7. Zinsser, H., and Mueller, J. H.: Nature of Bacterial Allergies, *J. Exper. Med.* **41**:159, 1925. Zinsser, H.: On the Significance of Bacterial Allergy in Infectious Diseases, *Bull. New York Acad. Med.* **4**:351, 1928.

8. Baldwin, E. R.: Studies in Immunity to Tuberculosis, *J. M. Research* **22**:189, 1910.

9. Krause, A. K.: Studies in Immunity to Tuberculosis, *J. M. Research* **24**:361, 1911.

The microscopic type of reaction was both polyblastic and exudative. The exudative reaction was more pronounced than in the normal and immune animals. Abscesses were common. All the larger nodules had abscesses in the centers. Many of the abscesses were large (fig. 1). The polyblastic type of reaction which was present in the smaller nodules did not differ in character from that found in the normal animals and in the animals immunized by intravenous injections of streptococci.

It should also be noticed that in only five of the twelve animals was there any agglutinating titer at the time of the secondary inoculations and in these the titer was not above 1:400. The agglutinating titer when the animals were killed was also low, never being above 1:400 and in one case it was absent entirely. It was evident that there was a decided hypersensitive state in this group of animals and that this

TABLE 4.—Results of Subcutaneous Injection of Streptococci into Hypersensitive Allergic Animals

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1.....	Many large	Many medium	0	0
2.....	Few small	0	0	200
3.....	0	0	0	200
4.....	Many small	0	0	200
5.....	Many large	Many small	0	200
6.....	Many large	Many small	0	200
7.....	Many large	Many small	0	200
8.....	Many large	Few small	200	400
9.....	Many large	Few small	200	400
10.....	Many large	Many large	400	400
11.....	Many large	Many large	400	400
12.....	Many large	Many large	400	400

hypersensitiveness was not dependent on a high humoral immunity, as indicated by the concentration of agglutinins, but depended on something in these animals which was not present or conspicuous in the first two groups. The conspicuous condition in group 3 which was absent in groups 1 and 2 was the primary abscess resulting from the injection with agar heavily seeded with streptococci. Something bound up with the abscess seemed to be responsible for the hypersensitiveness. This idea is in accord with the observations of Baldwin and Krause and the experiments of Swift and his co-workers. Just what this substance or condition is has apparently been determined by workers in immunity. It has been suggested by Zinsser and by Avery and Heidelberger¹⁰ that the protein of the organism is split up in the lesion and results in a changed antigen which stimulates the hypersensitiveness observed.

10. Avery, O. T., and Heidelberger, M.: Immunologic Relationships of Cell Constituents of Pneumococcus, *J. Exper. Med.* **42**:367, 1925.

COMMENT

Experimental streptococcic inflammatory lesions were studied by both gross and microscopic examination in animals under three specific conditions (normal, immune and hypersensitive, or allergic). The lesions studied were produced by the injection of small doses of streptococci into the subcutaneous tissues of the backs and sides of rabbits. These multiple small injections were spoken of as the multiple secondary injections or inoculations. The same doses were used in producing the



Fig. 1.—Subcutaneous nodules (abscesses) in a hypersensitive animal.

multiple subcutaneous lesions in all the animals in the three groups. The larger dose was $\frac{1}{100}$ of the sediment of a broth culture of streptococci, and the smaller dose was $\frac{1}{1000}$ of the sediment.

The first group of animals had not had any previous injection and showed no agglutinins for streptococci at the time of the multiple subcutaneous injections. These animals were the controls or normal animals. The second group consisted of animals which had been given an immunizing dose of streptococci intravenously. Most of these showed agglutinins in the blood at the time of killing and some at the time of

the secondary injections. The titers of the agglutinins varied according to the interval of time between the multiple subcutaneous injections and the intravenous injection. The animals of the second group were called the immune animals. The third group consisted of animals which had received one subcutaneous injection of agar at 45 C., heavily seeded with streptococci. Agglutinins in the blood of most of these animals were absent at the time of the secondary multiple subcutaneous injections and low at the time when the animals were killed. These animals were called the hypersensitive animals.

In the normal animals, few gross lesions were detected following the injection of either dilution. In the immune animals, when the subcutaneous inoculations were made before the seventh day after the immunizing inoculation, practically no lesions developed. Those animals in which the subcutaneous injections were made from the seventh to the twelfth days showed a greater frequency of lesions than did the normal animals. This greater reaction was probably due to an allergic reaction, since other animals highly immunized from several intravenous injections did not have this increased reaction. On the other hand, a retardation was shown. In the hypersensitive animals, gross lesions, often large abscesses, were practically always present with both the larger and the smaller doses. Abscesses were much more common in the hypersensitive animals than in the normal or the immune animals.

Two types of cellular reaction were noted in the nodules in all the experiments reported in this paper: (1) the exudative reaction, generally with necrosis and abscess formation, and (2) the polyblastic reaction. The cells chiefly found in the exudative reaction were polymorphonuclear leukocytes. In the polyblastic type of reaction, various cell types were seen, but the scarcity or absence of polymorphonuclear leukocytes was conspicuous. In the polyblastic lesions there were regular and irregular mononuclear and multinucleated cells with basophilic cytoplasm, plasma cells, eosinophils and lymphocytes. In some nodules, the more or less regularly shaped cells predominated. They gave the appearance of having wandered in (fig. 2). In other nodules, the cells were mainly irregular or elongated in shape and suggested that they might have developed from the existing cells in the region of the nodule (fig. 3).

The polyblastic type of microscopic cellular reaction was found in all three groups. No difference could be detected in the character of the reaction in the nodules. Polyblastic inflammation free from abscesses was less common in the hypersensitive animals, since the nodules were larger and the larger nodules regularly became abscesses.

It appears evident that the polyblastic type of reaction, which is characteristic of the lesions found in patients with acute rheumatic fever, does not depend primarily on a hypersensitive stage, when produced experimentally in animals. If doses sufficiently large are given,

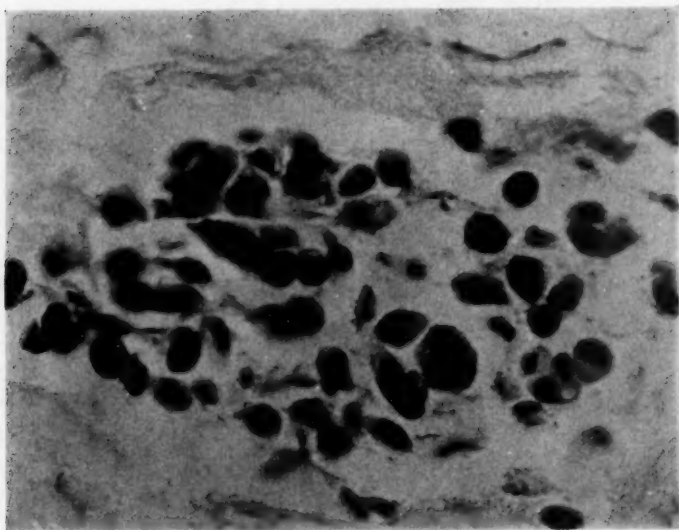


Fig. 2.—Microscopic structure of a subcutaneous nodule with polyblastic inflammation; $\times 450$. The cells appear to have wandered in.

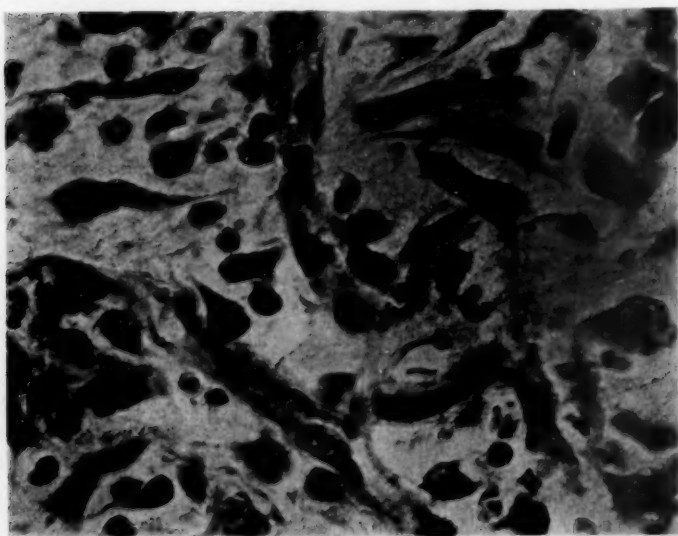


Fig. 3.—Microscopic structure of a subcutaneous nodule with polyblastic inflammation; $\times 450$. The polyblasts appear to have developed from existing cells in the area of the nodule.

this reaction may be produced in both normal and immune animals, as well as in hypersensitive animals.

It is evident, however, that doses which in normal or immune animals have no noticeable effect or produce only small, firm polyblastic nodules, will, in hypersensitive animals, stimulate the production of definite nodules, many of which are extensive enough to be abscesses. The relationship between allergy and the polyblastic type of reaction appears to be, as suggested by Maximow, a quantitative one. This quantitative relationship may help to explain the pathogenesis of human rheumatic lesion in many cases. Since streptococci have not been found in large numbers in the blood and joints of patients having acute rheumatic fever, it has been difficult to understand the extensive lesions; but when it is taken into account that very small doses of streptococci produce extensive reactions in hypersensitive animals and that high percentages of patients having acute rheumatic fever are hypersensitive to streptococci, the pathogenesis of the human lesions can more readily be understood.

SUMMARY

Experimental subcutaneous nodules with a polyblastic type of inflammation can be produced in normal, immune and allergic (hypersensitive) animals by regulating the dose of the injection.

Such nodules can be produced with much smaller doses in the hypersensitive animals.

General immunity, as indicated by a high agglutinating titer, tends to retard the development of subcutaneous nodules, except in cases in which the subcutaneous injections are made in from seven to twelve days after the primary immunizing inoculations. In these cases, the increased nodular production is probably due to allergy.

The larger nodules in all cases, as a rule, are abscesses; hence, the greater frequency of abscesses in the hypersensitive animals.

The relationship between allergy and the pathogenesis of experimental rheumatoid subcutaneous nodules appears to be quantitative only.

When these experimental results and the frequency of the hypersensitive state in patients with acute rheumatic fever are considered, it becomes less difficult to understand the pathogenesis of human rheumatic lesions.

CHRONIC PASSIVE CONGESTION OF THE LIVER

AN EXPERIMENTAL STUDY *

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The association between cardiac decompensation and hepatic cirrhosis has long been recognized. Kiernan's description, in 1833, of the "nutmeg liver" as the "second stage of congestion," has been followed by considerable controversy as to the etiologic factor or factors in the production of this pathologic picture. At the present time, it is believed by some that the central cirrhosis of the liver in cardiac decompensation is the result of necrosis of the liver cells around the central veins with a consequent shrinkage and condensation of the fibrous tissue normally present in that locality. Others believe that the destruction of the hepatic cells is followed, not by condensation of the fibrous tissue normally present, but by an actual proliferation of this tissue to produce the cirrhosis. Still others believe that not only does the factor of mechanical pressure play a part in the production of this picture, but a toxic agent, in addition, is necessary to cause a stimulation of connective tissue proliferation.

Unfortunately, these various opinions have been formed through the study of human autopsy material, and the little investigation that has been done on experimental animals has in the majority of instances been unsatisfactory.

Such observation of this condition has not been convincing as regards etiology, first, because it is impossible to rule out the toxic agent as a factor in the production of cirrhosis; secondly, because the lesions studied are most often, if not exclusively, the late rather than the early ones. Lambert and Allison¹ gave an excellent anatomic description of the changes in the liver usually associated with this condition and believed that the resultant central fibrosis is only an apparent increase in the amount of fibrous tissue due to condensation. Mallory² held the

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1. Lambert, R. A., and Allison, B. R.: Types of Lesion in Chronic Passive Congestion of the Liver, *Bull. Johns Hopkins Hosp.* **27**:350, 1916.

2. Mallory, F. B.: Chronic Passive Congestion of the Liver, *J. M. Research* **24**:455, 1911.

view that a toxic agent is a necessary adjunct in the production of the central fibrosis. The experimental work of Bolton³ is by far the most convincing. This observer produced experimentally a partial to complete obstruction of the inferior vena cava between the liver and the heart in animals and observed the central necrosis and condensation of fibrous tissue. He did not find active proliferation of the connective tissue cells.

The problem that presented itself to us was the production of a simple obstruction to the outflow of blood from the liver in dogs without the presence of any demonstrable toxic factor and the study of the mechanism of the production of changes in the liver structure over a long period of time.

EXPERIMENTAL TECHNIC

In general, the procedure used was to constrict by ligature the thoracic portion of the inferior vena cava to about one half of its normal diameter, and then, at stated intervals, to remove, through abdominal incisions, portions of different lobes of the liver for microscopic study. In all, sixteen dogs were used in the experiments, and several dogs had as many as four abdominal operations for the removal of portions of the liver.

In particular, the procedure was as follows: The dogs were placed under ether anesthesia by the ordinary "drop method." A "mushroom" catheter was then inserted into the trachea, the cap of this catheter entirely occluding the lumen and giving complete control of respiration for purposes of positive pressure. To the end of the catheter was attached a glass T-tube through which passed the air-ether mixture at a pressure indicated with a mercury manometer placed in the circuit. By alternately closing and opening the free end of the T-tube, both the rate of respiration and the depth could be accurately controlled. The operative procedure was to make an incision following the curve of the right sixth rib anteriorly. About 4 inches (10.16 cm.) of this rib, as close to the midline as possible, was then resected subperiosteally. The pleural cavity was entered and the right lung packed upward, exposing the inferior vena cava. The right phrenic nerve was then dissected free of this vessel for a distance of about 1 inch (2.5 cm.) and an aluminum band placed around the vena cava as close to the pericardial sac as possible with the apparatus devised by Halsted. The metal band was compressed digitally until the desired constriction of the vena cava was achieved. The parietal pleura and the intercostal muscles were sewed with a continuous catgut suture, the lung being freely expanded as the last stitch was taken. Interrupted sutures were used in the superficial muscles and on the skin. All the experiments that we shall report were made on animals that at no time showed evidence of infection.

RESULTS

Among the first of the problems that presented itself for solution was the extent of ligation of the inferior vena cava requisite for the production of chronic passive congestion. The venae cavae of three animals were ligated to produce a narrowing of the lumen to less than

3. Bolton, C.: The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, *J. Path. & Bact.* **19**:258, 1914-1915.

one-quarter the normal size, and in each instance the animal soon died: dog 1 at the end of eleven hours, dog 2 at the end of thirty hours and dog 3 at the end of sixty hours. From the time the animals recovered from the anesthesia until death, they vomited frequently and retched continuously. There were no signs of jaundice. The remainder had the vena cava ligated to about one-half its normal diameter and lived until killed.

Eleven Hours After Partial Ligation of the Inferior Vena Cava (About 90 Per Cent Occlusion).—About 100 cc. of blood-tinged fluid was present in the left pleural cavity and a somewhat less amount in the right. Petechial hemorrhages were present beneath the pleurae of both lungs and beneath the epicardium. The lungs were fully expanded. Approximately 1,000 cc. of bloody fluid was present in the peritoneal cavity. The stomach and intestines were markedly distended with gas. The liver was small, tense, deep red and congested. On section, there were present, throughout, dark red central areas surrounded by narrow borders of paler red columns of liver cells. None of the other abdominal viscera were congested.

Microscopic examination revealed diffuse necrosis of the whole liver. The columns of liver cells in the areas about the central veins were replaced by irregular pools of red blood cells, many of which were laked. The periphery of the hepatic lobules still showed the columnar and sinusoidal arrangement, but the liver cells were all devoid of nuclei. Indeed, field after field was viewed without one revealing a single nucleus, and this extensive necrosis involved the Kupffer cells and the perilobular connective tissue cells, as well as the hepatic cells.

Thirty Hours After Ligation of the Vena Cava (90 Per cent Occlusion).—About 50 cc. of a serosanguineous fluid was present in each pleural cavity and more than a liter of clear amber fluid in the peritoneal cavity. The aluminum band was in place around the vena cava and constricted this vessel to one-third its former diameter. The liver was tense and markedly congested.

Beneath Glisson's capsule were irregularly distributed small foci of widely dilated liver sinusoids which were engorged with well preserved red blood cells. Around the central veins there was necrosis of the liver cells, as well as of the endothelial cells lining the liver sinusoids, but the peripheries of the lobules showed no evidence of injury. The perilobular spaces were free from cellular infiltrations.

Sixty Hours After Ligation of the Vena Cava (90 Per Cent Occlusion).—In this animal, as in dog 1, vomiting and retching were prominent features following the operation. At necropsy, the lungs were found fully expanded, but they were congested. About 200 cc. of blood-tinged fluid was present in the right pleural cavity, and about

50 cc. in the left. The Halsted band around the inferior vena cava constricted this vessel about 90 per cent. In the abdominal cavity was present about 2,000 cc. of cloudy, serosanguineous fluid in which floated large flakes of gray fibrin. The liver was tense and deep red, and the liver lobulations were distinct even on external view. On section, the surfaces bled readily.

Again, the subcapsular liver sinusoids were engorged with well preserved red blood cells. There was hemorrhage into the parenchyma of the liver, most marked around the central veins. In these areas, the liver cells and the Kupffer cells, as well as the walls of the central veins, had entirely disappeared. Pools of blood of irregular outline occupied fully two thirds of each hepatic lobule and, lying in a central position in the lobule, replaced the normal architecture. These zones of hemorrhage were fringed by compressed liver cells which stained well and showed no nuclear disintegration. Already there could be seen delicate, spindle-shaped fibroblasts growing out into the central zones of hemorrhage. Mitotic figures or cellular exudates of any kind were absent. Occasionally, a sublobular vein was found the wall of which could just be distinguished, lying in a zone of necrosis.

Six Days After Ligation of the Vena Cava (50 Per Cent Occlusion).—Ascites was slow in onset, and at the time the animal was killed (with ether) no fluid was found in the pleural cavities, and only about 1,000 cc. of faintly blood-tinged fluid was present in the abdomen. This dog showed none of the vomiting and retching which the previous dogs displayed to so marked a degree.

As in the other animals, the liver was markedly congested and showed dark red central zones bounded by narrow borders of much paler tissue.

By far the best preserved liver cells were those which formed the columns immediately beneath the liver capsule, and that was in spite of the compression to which they were subjected by the greatly distended liver sinusoids. Several features were now present in addition to those already enumerated in the previous experiments. Mallory connective tissue stains showed a thickening by blue-staining connective tissue fibers of the walls of the central veins. In some places, this connective tissue proliferation had led to acini-like formation around these veins; large spaces resembling blood vessels lay here filled with the homogeneous pink-staining material of coagulated blood serum. Numerous mitotic figures were present in liver cells that formed the edges of the central zones of necrosis.

Nineteen Days After Ligation of the Vena Cava (50 Per cent Occlusion).—Nineteen days after the partial ligation of the inferior vena

cava, dog 9 was anesthetized with ether and a laparotomy performed. The abdomen contained over 3,000 cc. of clear yellow fluid. The liver was large and mottled red and yellow, resembling closely the "nutmeg liver." The surface was finely but irregularly granular, each granulation measuring no more than 2 mm. in diameter. A wedge-shaped piece of liver from the left lobe was removed with the electric cautery for microscopic examination.

The process of central fibrosis was gradually increasing in extent. Spindle-shaped fibroblasts were present in the center of each hepatic lobule and completely replaced liver cells, as well as endothelial cells. (Necrotic liver cells were still seen bordering these areas of fibrosis.) Zones of newly formed but greatly dilated vessels were seen around each central vein in the loose connective tissue.

Sixty-One Days After Ligation (50 Per Cent Occlusion).—Once more dog 9 was anesthetized with ether and a laparotomy performed. The abdomen was free from excess fluid. The collateral venous circulation in the anterior abdominal and thoracic walls was not established to any marked degree. The retroperitoneal veins were small. The scarring of the liver noted at the end of nineteen days had progressed, and now the external surfaces were coarsely and irregularly granular. Again, a wedge-shaped piece, this time from the right lobe, was removed with the electric cautery.

From the histologic picture, it was at once apparent that the fibrosing process had progressed in the interval of twenty-two days. The central fibrotic areas now involved fully two thirds of each hepatic lobule. Narrow bands of liver cells containing large fat granules were present at the periphery of each lobule. The connective tissue was more dense in structure and stained a brilliant blue with the aniline blue stain. There was a marked increase in the size of the vascular channels in this connective tissue, many of them being several times larger than the central veins themselves. Occasionally, they were filled with red blood cells, but more often they contained homogeneous coagulated material, and then they appeared as tortuous cystlike formations. Often, strands of connective tissue from the central areas extended to the capsular surface and appeared to draw the capsule in, producing indentations which in the gross appeared as the depressions between the granular nodules. The liver sinusoids beneath the capsule were dilated to such a degree as to be several times the diameter of the largest central veins. There was no evidence of a cellular reaction of the exudative type anywhere in the many sections studied.

Sixty-Three Days After Ligation (50 Per Cent Occlusion).—A laparotomy was performed on dog 14 following a partial ligation of the

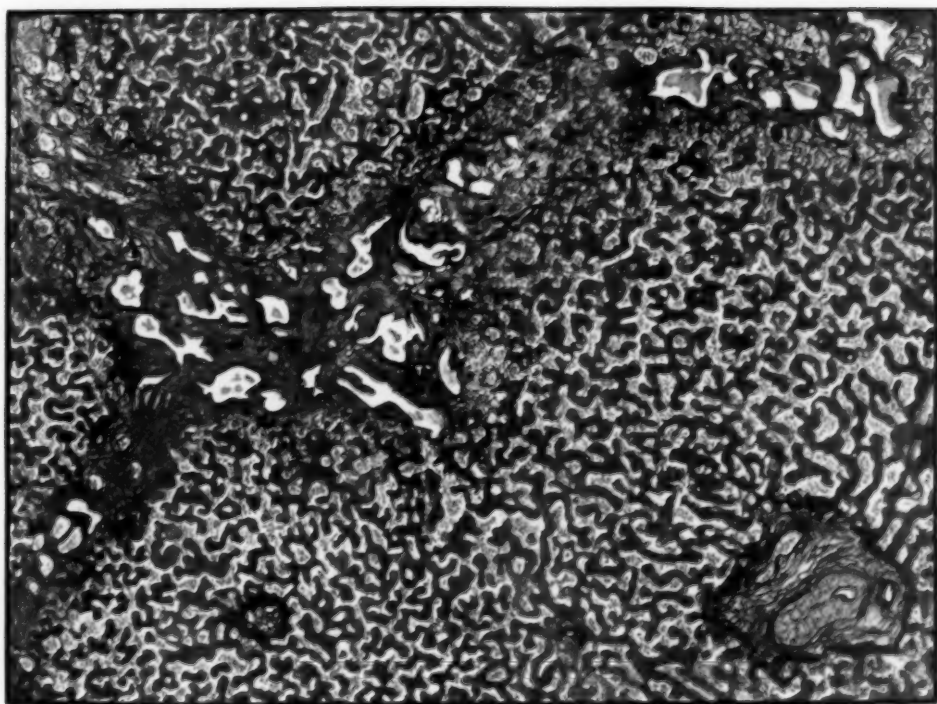


Fig. 1.—Drawing of an area about a central vein, magnified 93 times to show the scar tissue and the pseudocyst formations.

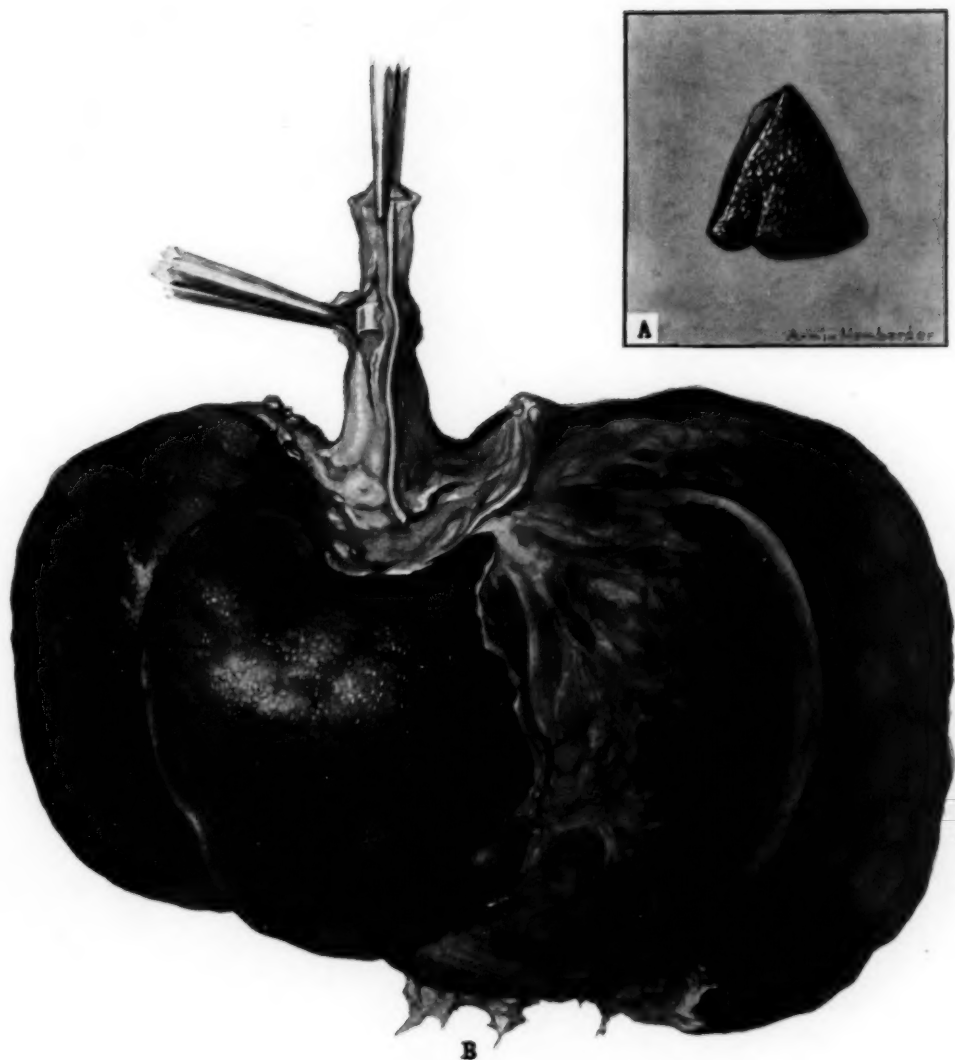


Fig. 2.—*A*, wedge-shaped piece of liver removed sixty-three days after the partial ligation of the inferior vena cava. Note the finely granular surface. *B*, liver of dog the vena cava of which was partially ligated 137 days previously. Note the metal band around the inferior vena cava and the scarring of the liver.

inferior vena cava sixty-three days previously. The abdominal cavity contained a little over 3,000 cc. of straw-colored fluid stained with blood pigment. The external surfaces of the liver were moderately granular (fig. 1), these granules being either deep purple or light red. Those lighter in color were of a much softer consistency. The liver cut with increased resistance. A portion of the left lobe was removed with the electric cautery.

In general, the histologic picture (fig. 1) was similar to that described for the forty-one-day experiment, with the following additions: The subcapsular venous sinuses were dilated to a degree similar to that seen in the areas around the central veins, and there was also an apparent though slight increase in the connective tissue in this location, but whereas in the central areas the fibrosis was the result of an active proliferation of connective tissue, that in the subcapsular areas was at best in great part due to a shrinkage or disappearance of the hepatic cells by compression, with a consequent predominance of connective tissue.

*Eighty-Five Days After Ligation (50 Per Cent Occlusion).—*Twenty-two days after the last laparotomy, dog 14 was again explored, and it was found that over 2,000 cc. of slightly blood-tinged fluid had reaccumulated in the peritoneal cavity. The liver surfaces were mottled dark red and pale bright red, and they were also granular. A portion of the right lobe of the liver was removed by knife, and then the bleeding surfaces were cauterized with an electric cautery.

A rather surprising microscopic observation was the numerous hemorrhages into the parenchyma of the liver occupying subcapsular and midzonal positions. As the centers of the hepatic lobules were occupied by dense scar tissue and pseudocysts, the hemorrhagic foci lay on the periphery of these scarred zones. The walls of the central veins were increased in thickness three or four times.

*One Hundred and Thirty-Seven Days After Ligation (50 Per Cent Occlusion).—*Dog 14 was killed with ether at the end of 137 days after the ligation of the inferior vena cava. This time, the abdomen was free from excess fluid. To a small area on the superior surface of the liver (fig. 2) were adherent dense fibrous tags which bound it to the operative scars in the anterior abdominal wall. All surfaces of the liver were mottled with alternating dark red and bright red patches which varied in size from 2 mm. to 1.5 cm. in diameter. Coarse and fine granulations covered all the surfaces of the liver. On section, the bright red mottlings appeared to be beneath the capsule for only short distances. The inferior vena cava was constricted about 50 per cent by the metal band that lay embedded in newly formed connective tissue. There was no free fluid in either pleural cavity.

The liver capsule was not thickened. Beneath it could be seen dilated venous sinusoids engorged with red blood cells. The parenchymal structure was maintained here, but the columns of liver cells were compressed. Dense bands of connective tissue followed sublobular veins to the capsule and drew it in with the resultant formation of the granulations noted grossly. The process apparently had ceased to be progressive, as no hemorrhage, necrosis or cellular division was present.

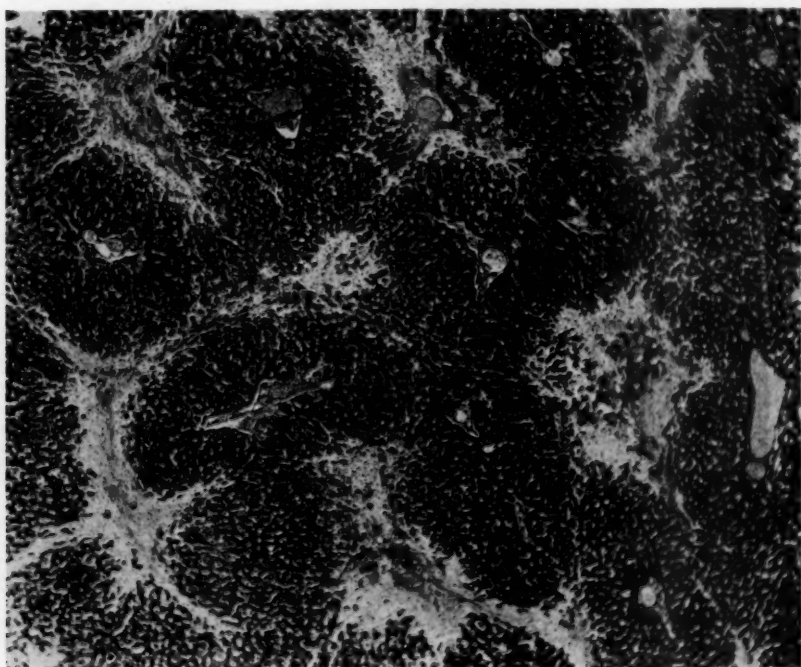


Fig. 3.—Photomicrograph showing the extensive scarring in areas about the central veins, which produces a false lobulation of the liver. This condition occurred in the liver of a dog the inferior vena cava of which was partially ligated 216 days previously. Hematoxylin and eosin stain; $\times 60$.

Two Hundred and Sixteen Days After Ligation (50 Per Cent Occlusion).—Dog 15 was killed with ether 216 days after the ligation was performed. Both pleural cavities and the abdomen were free from excess fluid. The metal band constricted the inferior cava about 50 per cent. The external surfaces of the liver were coarsely nodular and looked not unlike those in the 137-day experiment. In the hope of determining the relationship between the pseudocysts and the central veins, a mixture of barium sulphate was injected into the liver through the inferior vena cava at a pressure of 100 mm. of mercury, and on

microscopic examination this mixture was seen to fill both the central veins and the pseudocysts—a fact which proved their direct communication.

Closer examination showed dense scar tissue in the areas about the central veins, often extending from one lobule into another and producing lobulations in the liver which had in their centers the periportal zones surrounded by normal liver cells (figs. 3 and 4). The picture

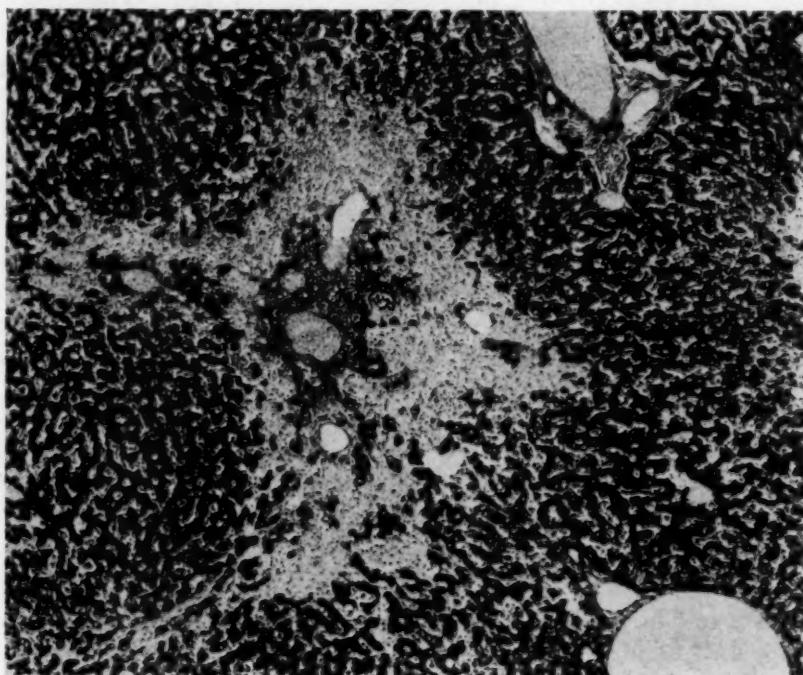


Fig. 4.—More detailed view of the scar tissue in the area about a central vein from the same liver as that shown in figure 3. Hematoxylin and eosin stain; $\times 225$.

was similar to that seen in periportal cirrhosis or fibrosis, except that the fibrous tissue in this condition lay in a different part of the liver lobule.

COMMENT

It is important to consider how far these experiments parallel the condition of chronic passive congestion so often seen at the bedside. If it is at all permissible to compare lesions produced in experiments on animals with those found in man, then we may argue that the obstruction to the inferior vena cava is effective in producing consequences in

the dog that a failure of the right side of the heart produces in man. If the obstruction is of such a degree only as to produce gradual congestive phenomena, then these experimental conditions approach all the more closely those existing in heart failure. In thirteen of the sixteen animals of these experiments, the obstruction was relatively slight (about 50 per cent), and the resultant ascites was gradual in onset. Also, the lesions found in the livers of these animals never involved more than the immediate pericentral areas. In three of the sixteen dogs in whom the obstruction was much greater (about 90 per cent), all the signs of congestive failure were almost immediate in onset and the hepatic necrosis involved nearly all of the hepatic lobule throughout the liver. It is, perhaps, necessary to point out that even in these three animals there was no question of infarction of the liver, if by that term we mean necrosis resulting from the interference with the blood supply to an organ or a part of one. And yet it is readily admitted that the rapid course of the condition in these animals does not parallel that of persons dying from congestive heart failure. It must be pointed out also that in all our experiments the lesions were steadily progressive, even when gradual, and did not show the periods of apparent arrest or improvement which are so often observed clinically in persons with congestive heart failure.

It seems safe to assert that the lesion produced in these experiments was the result of a simple mechanical interference with the venous return from the liver, and that a toxin, particularly one liberated in the course of an infectious process, had no part in the production of this lesion.

SUMMARY

Necrosis of the liver follows simple mechanical obstruction to the outflow of blood, the extent of the necrosis being proportional to the amount of obstruction. The necrosis can involve the whole liver eleven hours after the ligation of the inferior vena cava.

Ascites is early associated with necrosis of the liver, which is consequent to the obstruction of the inferior vena cava.

As early as six days after the partial ligation of the inferior vena cava there is evidence in the liver of repair, as manifested by the numerous mitotic figures and the increase in the connective tissue in the areas around the central veins.

Nineteen days after partial ligation of the inferior vena cava, the liver shows grossly the picture of chronic passive congestion. Active proliferation of connective tissue is seen around the central veins.

In forty-one days there are marked distention of the subcapsular venous sinusoids and marked fibrosis of the areas about the central veins, with large vascular spaces newly formed in this scar tissue.

The cystlike formations in the connective tissue around the central veins are branches of these vessels.

The fibrosis ceases to increase in extent after eighty-five days and is essentially of the same extent 216 days after the ligation of the inferior vena cava.

Central fibrosis of the liver can result without infection being present, and is due to an active proliferation of connective tissue.

MECONIUM PERITONITIS FROM SPONTANEOUS PERFORATION OF THE ILEUM IN UTERO*

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The pathology of the fetus is still a relatively new field. The anomalies and maldevelopments have been thoroughly investigated, but from the point of view of primary developmental aberrations. There has developed recently, however, a new point of view emphasizing that not all fetal anomalies are due to developmental disturbances and that not all fetal diseases are of maternal origin. It is gradually becoming recognized that the same factors causing disease in extra-uterine life are operative also in utero. Thus, intestinal obstruction, perforation of the intestines and peritonitis are equally explained by incarceration in hernias, strangulation by bands, intussusception, etc. The study of the pathology of the fetus has cast much light on fetal physiology and vice versa. Though a considerable literature has accumulated relative to the question of fetal peritonitis, many problems still remain unsolved, and further observations casting some light on the problem warrant publication. For this reason I have thought it worth while to report a case of meconium peritonitis which I have had the opportunity to study and to review the literature with reference to this subject, especially as the conditions present at the site of the perforation in the intestine permit an explanation not as yet offered.

Meconium peritonitis is a pathologic entity which is to be clearly differentiated from the acute bacterial peritonitis of the new-born occurring as a complication of infections of the cord, septicemia of maternal origin, syphilis (Baumgarten¹) or similar conditions. By meconium peritonitis is meant a nonbacterial foreign body and chemical peritonitis occurring during intra-uterine life as the result of abnormal communication between the bowel contents and the peritoneal cavity. As already emphasized by Gierke,² the term meconium peritonitis is only applicable to those cases in which there is demonstrable within the peritoneum, meconium, calcified meconium, mucous droplets,

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* From the Pathological Laboratories of the Cook County Hospital.

1. Baumgarten, cited by Peiser, A.: Die fötale Peritonitis; eine klinische Studie, Beitr. z. klin. Chir. **60**:168, 1908.

2. Von Gierke, E.: Bauchfell, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1, p. 1069.

foreign body giant cells, cells from the source of perforation, fibrinous or fibrous adhesions and, rarely, lanugo hair.

In the comment on the etiology it will be seen that although the conditions favorable to an intestinal perforation may arise early in intra-uterine life, the actual perforation may take place during labor or shortly afterward as a result of the increased peristalsis during this time and of the mechanical forces of the labor itself. Of course, such cases are not purely of a mechanical or chemical nature, as within from three to six hours the originally sterile intestinal contents become infected and there is then superadded a bacterial etiology for the peritonitis (Escherich,³ Kendall⁴). But a comprehensive conception that attempts to explain intra-uterine rupture should also explain intrapartum and immediately postpartum bowel ruptures, especially, since the time of rupture is extremely variable. The term, meconium peritonitis, therefore, should be applied to cases resulting from fetal or intrapartum or shortly postpartum intestinal rupture.

Meconium is a sterile mixture of cast off epithelial cells, bile pigment, bile salts, cholesterol, fat, stearic acid, sebaceous material from swallowed liquor amnii, mucin and salts (Williams,⁵ Sturzenegger⁶). Bile and its constituents are formed at about the end of the third month (Zweifel,⁷ Kölliker,⁸ Prentiss and Arey⁹). Pancreatic and gastric secretions with their enzymes are added at about the fifth month, perhaps earlier (Langendorff¹⁰ and Zweifel⁷).

The existence of peristalsis within the fetus is necessary for the production of intestinal rupture. There is no direct observational evidence, but certain facts presuppose the existence of peristalsis early in fetal life. The presence of meconium in the cecum was observed by

3. Escherich, T.: *Die Darmbakterien der Säuglinge*, 1886; cited by Peiser (footnote 1).

4. Kendall, A. I., cited by Michael, May, in Abt, I. A.: *Pediatrics*, Philadelphia, W. B. Saunders Company, 1923, vol. 7, p. 31.

5. Williams, J. W.: *Obstetrics*, New York, D. Appleton & Company, 1926, p. 392.

6. Sturzenegger, E.: *Ein Fall von Mekonium Peritonitis mit Verhalkungen in Peritoneum und Myocardium*, *Beitr. z. path. Anat. u. z. allg. Path.* **78**:85, 1927.

7. Zweifel, H.: *Untersuchungen über das Meconium*, *Arch. f. Gynäk.* **7**:474, 1875.

8. Kölliker, A.: *Development of the Intestine*, in Keibel and Mall: *Human Embryology*, Philadelphia, J. B. Lippincott Company, 1912, p. 390.

9. Prentiss and Arey: *A Laboratory Manual and Textbook of Embryology*, Philadelphia, W. B. Saunders Company, 1923, p. 179.

10. Langendorff, cited by Landsteiner, K.: *Darmverschluss durch eingedichtetes Meconium; Pancreatitis*, *Centralbl. f. allg. Path. u. path. Anat.* **16**:903 (Nov. 30) 1905.

Mall¹¹ in a 130 mm. embryo. Broman¹² believed that the progressive course of the meconium was a factor in the development of the intestines, especially of the rectum and anus. He pointed out that anomalous communications of the small intestine or the cecum which diverted the meconium were almost regularly associated with atresia of the rectum and that the bowel below an atresia formed a firmly contracted string with a pinpoint lumen. Cases of fetal intussusception, as well as of incarceration of a loop of ileum in a hole in the mesentery of the jejunum, point to an early onset of peristalsis; similarly, the presence of marked dilatation and hypertrophy of the intestine above a constriction with thinning out at the site of constriction allow the same conclusion. Meconium, therefore, as it is formed at about the third month acts as an irritant or stimulus to peristalsis, which drives the meconium down and progressively aids in the proper development of the intestine.

The earliest time of onset of meconium peritonitis cannot, of course, be determined with any accuracy. Silberman¹³ placed the period in the first third of fetal life and Mackenrodt,¹⁴ among others, in the second third. In a case reported by Rudnew,¹⁵ a dead fetus of 6 months showed a membrane 2 mm. thick adherent to the intestines, with calcified plaques throughout the peritoneum. The amount and the stage of organization of the meconium and the reactive exudate are of value in estimating the duration of the peritonitis. Calcification is not as valuable, since as shown by Litten,¹⁶ the latter may take place within twenty-four hours. From Rudnew's case, one may say that fetal peritonitis may commence earlier than the sixth month, and in most cases, probably in the period between the third and the sixth month.

The reactive phenomena resulting on the entrance of meconium into the peritoneal cavity are those of a chemical and foreign body peritonitis. Dense adhesions and calcified plaques are formed as end-results. The calcification of the meconium is, no doubt, due to the precipitation of the calcium of the tissue fluids and the blood by the broken down fatty constituents. There occasionally occurs not only local but also distant calcification. Sturzenegger⁶ described a case of fetal peritonitis in

11. Mall, F. P., in Keibel and Mall (footnote 8, p. 390).

12. Broman, cited by Koch, W.: *Missbildungen von Verengerungen und Verschlüsse*, in Henke, F., and Lubarsch, O. (footnote 2, p. 189).

13. Silberman, O.: *Ueber Bauchfellentzündung Neugeborener*, *Jahrb. f. Kinderh.* **18**:420, 1882.

14. Mackenrodt, A.: *Berichte aus gynäkologischen Gesellschaften und Krankenhäusern*, *Zentralbl. f. Gynäk.* **16**:654, 1893.

15. Rudnew, W.: *Ueber die spontanen Darmrupturen bei Foeten und Neugeborenen*, *Inaug. Dissertation*, Basel, 1915.

16. Litten, cited by Rudnew (footnote 15).

which the myocardium was extensively calcified. His explanation for these distant metastases is unsatisfactory. He assumed an alkalination of the circulating blood and of the tissue fluids as a result of absorption of alkaline salts from the meconium within the peritoneum (Hofmeister¹⁷).

REPORT OF A CASE

Maternal History.—The mother was a colored woman, aged 21. It was her first pregnancy. The period of gestation had been normal, and physical examination at the time of entry revealed no abnormality. The first stage of labor was of ten hours' duration, and the infant was delivered thirty minutes after full dilatation. Parturition was uneventful. The Wassermann reaction of the blood before and after labor was negative.

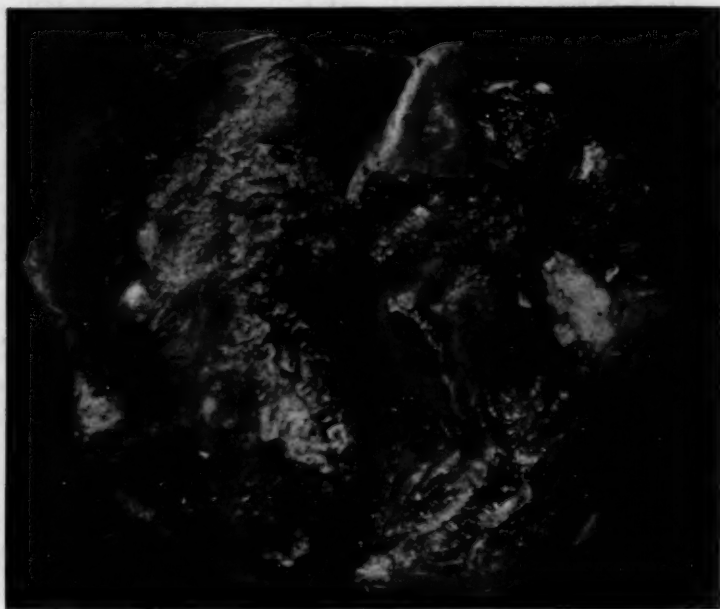


Fig. 1.—Marked thickening of the capsule of the spleen with adherent calcified meconium plaques.

Infant.—The infant was full term. Physical examination shortly after birth revealed a markedly distended abdomen which was tympanitic anteriorly and dull in the flanks. There was evidence of compression in both lower pulmonary lobes. There was an easily reducible left inguinal hernia.

The labia majora were slightly edematous. Catheterization of the rectum yielded a large amount of gas. The Wassermann reaction of the blood was negative. The child was fed by breast six times a day at three hour intervals, and water and protein milk were given between feedings. Within twenty-four hours,

17. Hofmeister, F.: Ueber Ablagerung und Resorption von Kalksalzen in den Geweben, *Ergebn. d. Physiol.* **10**:429, 1910.

the infant began to regurgitate all food and water and became markedly cyanotic. The distention of the abdomen had increased markedly. Râles were heard in the chest. The rectum prolapsed slightly. The infant became comatose and died twenty-six hours after birth.

Postmortem Examination.—The body was that of a full term, well nourished female infant. The abdomen was markedly distended. There was a left inguinal, easily reducible hernia.

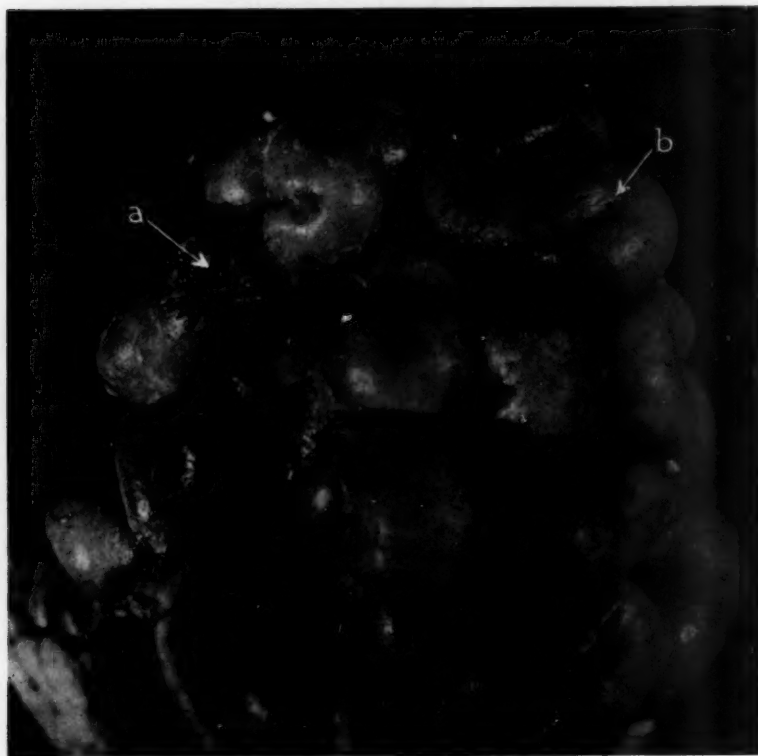


Fig. 2.—Perforation in the lower ileum (a) with nodules about the perforation and (b) dense fibrous adhesions.

The pleural surfaces were bright and glistening. The lungs were light red, the basal portions purplish. The upper lobes were crepitant, the lower lobes subcrepitant, and the cut surface purplish pink. The heart was normal.

The abdominal cavity contained about 150 cc. of a brownish, cloudy fluid in which were suspended yellowish flakes. The loops of the small intestine were matted together into a solid mass about 8 cm. in diameter by fine strands which broke easily. The loops were moderately distended by gas and meconium. The serosa was a light pinkish gray and covered by numerous firmly adherent, finely granular, light yellowish-gray masses. These masses were also found on the surface of the liver and spleen (fig. 1). On the inferior aspect of the liver, they

reached a maximum thickness of 2 mm. On the anterior aspect of the spleen, they were as much as 25 mm. in diameter. The duodenum was drawn toward the hilus of the liver and attached rather firmly to the gallbladder.

In the ileum about 60 mm. above the junction with the colon on the inferior aspect and near the mesenteric attachment there was an opening in the intestinal wall, 1 mm. in diameter (fig. 2).

From this opening, thick, greenish material and mucus exuded on pressure. The lower part of the ileum felt rather firm and, adjacent to the opening, there was a soft, light-red nodule, 2 mm. in diameter.

The spleen was large, soft and friable. The pulp was a deep red and showed no structure.

The liver weighed 90 Gm. and was moderately firm. The surface was smooth, except for the yellow deposits previously described. The cut surface was brownish gray; the markings were obscure.

The kidneys weighed 20 Gm.; the surface was smooth and light gray-brown. On section, the medulla was deep red.

The pelvic organs were normal. The ovaries were deep red.

The brain showed no anomalies.

Microscopic Examination.—Sections were made of all the organs. In addition, serial sections were made of the bowel, including transverse sections immediately above and below the site of perforation and longitudinal sections through the perforation. The sections were 5 microns thick, and every fifth section was stained. Those immediately above and below and those through the perforation were taken at three section intervals. For comparison, serial sections were made of every portion of the large and small intestine of three newly born full term infants who died of cerebral injuries and presented no anomalies. Hematoxylin and eosin were used throughout, with Levaditi and Giemsa stains on selected tissues.

The acinar structure of the liver was well preserved. The sinusoids were dilated and filled with blood. There were numerous intra-acinar and intracapillary areas of erythropoietic and granulopoietic tissue. The liver cells were large, their nuclei pale and vesicular. There was a moderate periportal infiltration of lymphocytes and granulocytes. Calcareous particles were adherent to and encased within the markedly thickened capsule.

The suprarenal glands presented a slight hyperemia of the zona reticularis.

The heart revealed no abnormality.

The follicles of the thyroid gland were both large and small and lined by cuboidal cells and filled with a well staining colloid. The blood vessels were markedly dilated.

The peritoneal part of the diaphragm was markedly thickened and infiltrated by histiocytes, fibroblasts, multinucleated giant cells and lymphocytes.

The kidneys showed focal areas of interstitial infiltration composed of lymphocytes. In the center of one of these infiltrations was a convoluted tubule with two layers of epithelium. Externally, there was a layer of elongated cells, and the internal layer was formed by large cuboidal cells with huge, round, deeply stained nuclei.

The vessels of the mesentery were patent and of normal structure.

The pancreatic acini were well developed. The islands were large and numerous. The interstitial tissue was of moderate amount. There were numerous interlobular and intralobular accumulations of lymphocytes. In the peritoneal lining were numerous, bluish, granular clumps, histiocytes, round cells and giant cells.

The malpighian corpuscles of the spleen were small. The sinusoids were indistinct, and there was much blood within the pulp, which was moderately cellular. The capsule was thick and edematous, and there were numerous dark blue, granular clumps scattered throughout. The deeper part of the capsule was invaded by new-formed capillaries, fibroblasts and eosinophils.

The ovary showed a large number of primitive follicles and a distinct capillary dilatation.

The brain presented no abnormality.



Fig. 3.—Transverse section just lateral to the perforation showing (a) absence of longitudinal muscle layer and marked thinning of the circular layer, large amount of lymphatic tissue in the submucosa and (b) deeply penetrating crypts of Lieberkühn, which rest directly on the muscularis; $\times 150$. Hematoxylin and eosin stain.

Sections of the intestines through areas other than those immediately above, below or through the perforation showed nothing abnormal. The lymphoid tissue was normal in amount. The perivascular muscle gaps were located mainly along the mesentery in the small intestine and lateral to the taenia mesenterica in the large intestine. Occasional gaps occurred on the antimesenteric side of the small

intestine. These were normal when compared with the control sections. Longitudinal sections through the perforation showed the following matters of interest: Lateral to the perforation, the muscle layers were well preserved, but there was noticeable an excessively large amount of lymphatic tissue in the submucosa which broke up the muscularis mucosa over large areas. Directly lateral to the perforation, the muscle layer suddenly thinned out, and the longitudinal layer disappeared. The lymphatic tissue here became still more marked in amount, and the mucosal glands penetrated this tissue and rested directly on the muscularis (fig. 3). The circular muscle became progressively thinner and thinner

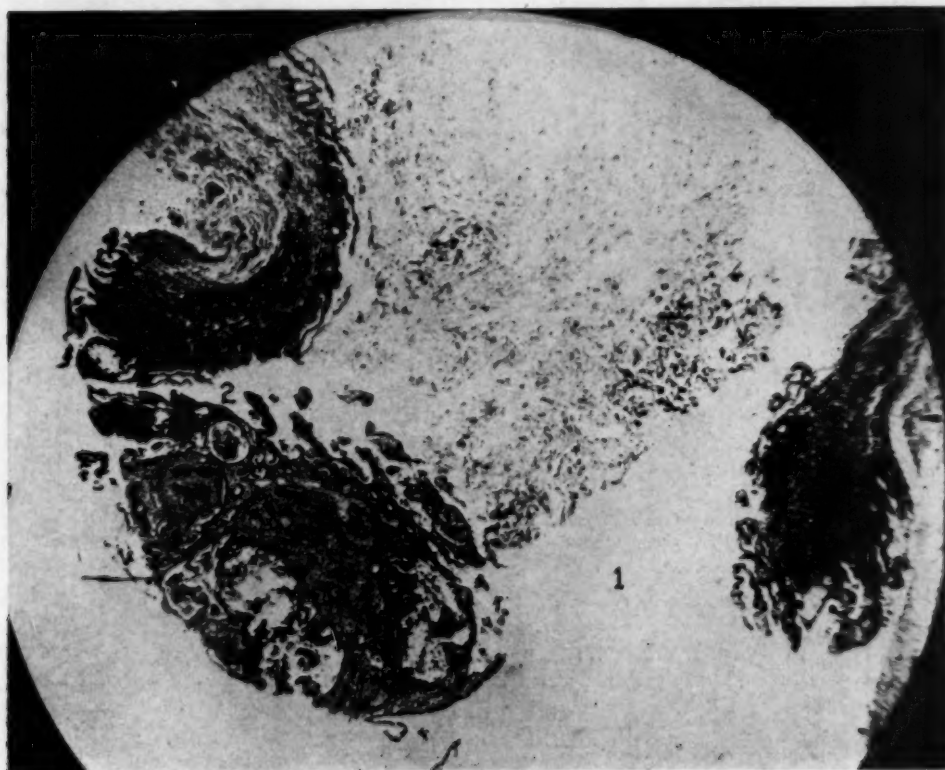


Fig. 4.—Longitudinal section through perforations showing (1) the major perforation bounded by lymphatic nodules covered by cystic glands and (2) the small perforation through a section of intestine in which the muscularis is absent and the lymphatic tissue and glands are excessively developed; $\times 35$. Hematoxylin and eosin stain.

as the lymphoid tissue increased. The next section showed an outpouching of the wall composed of glands and lymphoid tissue. In the next section, this outpouching had ruptured, and the mucosa was reflected sleevelike about the opening. In this reflected portion, the intestinal glands were large and cystic. Within these cystlike structures, granular debris and polymorphonuclear leukocytes could

be seen. In the next few sections, another perforation was seen at the margin of the reflected portion. This perforation was bounded by lymphatic tissue deeply penetrated by crypts of Lieberkühn. There was no underlying muscle tissue (fig. 4). The succeeding sections showed the main perforation bounded by huge lymphoid masses covered by cystic glands. As the muscle tissue approached the perforations, it ended abruptly (fig. 5). Serial transverse sections immediately below the sites of perforation revealed a large amount of lymphatic tissue. The latter occupied more than two thirds of the circumference, and in places the glands of Lieberkühn were seen to penetrate this tissue down to the muscularis (fig. 6). This was not to be found in the sections immediately above

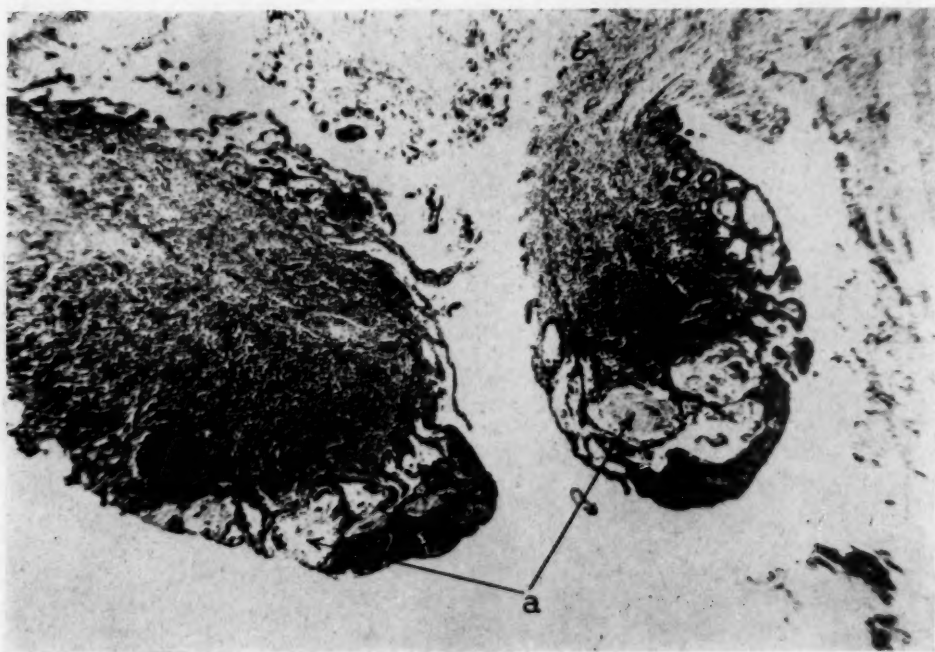


Fig. 5.—Longitudinal section through middle of perforation showing large lymphatic nodules and (a) cystic glands; $\times 45$.

the perforation nor in the sections of this region taken from other infants. Smears from the peritoneal exudate showed a few gram-positive cocci. Levaditi stains of pancreas, kidney and liver were negative for spirochetes.

Summary of Microscopic Examination: In addition to a chronic meconium peritonitis with calcification and advanced fibrosis, the outstanding features at the sites of perforation were excessive development of lymphatic tissue, deeply penetrating intranodular crypts of Lieberkühn, circumscribed disappearance of the longitudinal muscle layer with marked thinning of the circular layer, cystic dilatation of glands of the reflected portions of the intestinal wall and intralymphatic gland proliferations in the segment of intestine immediately below the perforations.

Anatomic Diagnosis.—Spontaneous intra-uterine perforation of the lower ileum with eversion of the mucosa; local hyperplasia of the lymphatic tissue at the point of and below the site of perforation with intranodular gland proliferation; ancient meconium peritonitis; focal interstitial chronic nephritis and pancreatitis; chronic tumor of the spleen; compression atelectasis of the basal parts of both lungs; erythropoiesis and granulopoiesis in the liver; left inguinal hernia.

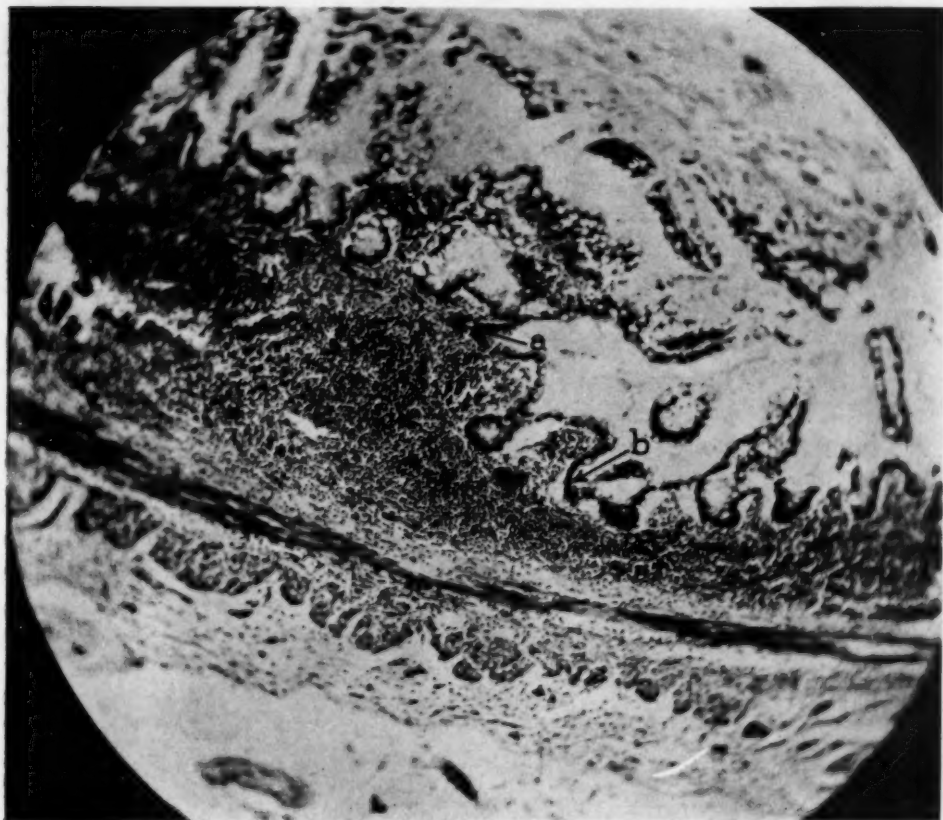


Fig. 6.—Transverse section through intestine immediately below the perforation showing (a) the large amount of lymphatic tissue and the abruptly interrupted muscularis mucosa and (b) the deep penetration of the former by the crypts of Lieberkühn.

COMMENT

There are numerous factors in the causation of rupture of the intestine in utero. For the purposes of discussion they will be divided into the group associated with obstruction and that without.

Cases with Obstruction.—A large percentage of cases of fetal peritonitis are associated with some form of intestinal obstruction.

Thus of 40 cases of meconium peritonitis reported by Rudnew,¹⁵ 22, or more than 50 per cent, were associated with stenosis or atresia of the intestine. As to which is cause and which effect would seem to offer little difficulty from an analysis of the relative frequency. In 1922, Davis and Poynter¹⁸ collected 392 cases of intestinal occlusion (exclusive of rectal) without intestinal perforation. In 103 similar cases, Kreuter¹⁹ found only 10 cases of peritonitis. The explanation of intestinal occlusions has been rather unsatisfactory, as can be gathered from the multiplicity of causes cited. Thus Kuliga,²⁰ Sella,²¹ Peiser,²² Davis and Poynter¹⁸ mentioned intussusception, volvulus, vascular maldevelopment, external bands, enteritis, fusion of Kerkring's folds and epithelial proliferation (in the duodenum Tandler²³ and in the small intestine Kreuter¹⁹ and Forssner²⁴). It is therefore not surprising that fetal peritonitis has been also mentioned as a possible cause (Fiedler²⁵ and Theremin²⁶). This is obviously wrong, as can be gathered from the foregoing statistics. Complete resolution of peritonitis is impossible. Isolated peritoneal bands are reported in the literature (Flesch²⁷) as evidence of fetal peritonitis. These are without doubt developmental and not inflammatory in origin.

The sites of predilection of stenoses and atresias are: duodenum (34 per cent), upper small intestine (15 per cent), ileocecal region (25 per cent), colon (10 per cent) and multiple locations (10 per cent) (Davis and Poynter¹⁸). These figures are somewhat variable (Kuliga,²⁰

18. Davis, D. L., and Poynter, C. M. W.: Congenital Occlusions of the Intestines with Report of a Case of Multiple Atresia of the Jejunum, *Surg. Gynec. Obst.* **34**:35 (Jan.) 1922.

19. Kreuter, E.: Die angeborenen Verschlüssungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte, *Deutsche Ztschr. f. Chir.* **79**:1, 1905.

20. Kuliga, P.: Zur Genese der kongenitalen Dünndarmstenosen und Atresian, *Beitr. z. path. Anat. u. z. allg. Path.* **33**:481, 1903.

21. Sella, U.: Ueber kongenitale Atresia des Darmes und der weiblichen Genitalen und ihr Verhältnis zur fötalen Peritonitis, *Beitr. z. path. Anat. u. z. allg. Path.* **53**:243, 1912.

22. Peiser, A. (footnote 1).

23. Tandler, J.: Zur Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien, *Morphol. Jahrb.* **29**:187, 1902.

24. Forssner, H.: Die angeborenen Darm und Oesophagus Atresien, *Anat. Hefte* **34**:1 (July) 1907.

25. Fiedler, cited by Theremin, E.: Ueber kongenitale Occlusionen des Dünndarms, *Deutsche Ztschr. f. Chir.* **8**:34, 1877.

26. Theremin, E. (footnote 25).

27. Flesch, H.: Beitrag zur Frage der fötalen Peritonitis, *Jahrb. f. Kinderh.* **108**:366 (May) 1925.

Braun,²⁸ Farr and Brunkow²⁹). They are exclusive of rectal strictures, which are from one to four times as numerous as all the other occlusions together.

An analysis of cases of intestinal obstruction associated with perforation shows that the latter generally occurs just proximal to the obstruction, except in strictures of the rectum, in which the rupture is variably situated from cecum to sigmoid. The mechanism of perforation in these cases varies. The active peristalsis above an obstruction produces thinning and perforation, whereas volvulus compromises the blood supply with resulting necrosis and perforation.

Cases of fetal peritonitis have been described with every type of intestinal occlusion. Intussusception in the lower ileum was observed by Chiari,³⁰ Sella³¹ and Ciechanowski and Glinski;³¹ volvulus of the small intestine by Nötterbrock³² and Sturzenegger;⁶ simple atresia and rupture by Krokiewicz,³² Martens³³ and recently Westphal.³⁴ Obstruction by peritoneal bands is frequent. Pfaff³² observed a band which bound the hepatic flexure to the gallbladder and caused a rupture of the distended ascending colon. A complete severance of a loop of intestine by a constricting band with perforation of the proximal dilated segment was described by Mackenrodt.¹⁴ These bands are no doubt of developmental origin, and are related to atrophied prolongations of Meckel's diverticulum, incompletely obliterated fetal mesenteries, etc. Valvelike occlusion of the lumen by mucosal folds with rupture proximally was found in the rectum by Browicz³² and in the ileum by Loebisch.³² Angulations of the intestine are responsible for still other cases as reported by Ciechanowski,³¹ in whose case a sharply angulated transverse colon ruptured proximal to the angulation. Rudnew¹⁵ and Heyn³² mentioned cases of kinked loops of the ileum which led to perforation. The origin of these bands and kinks is to be attributed to torsion and maldevelopment of the mesenteries. Imperforate anus has led to innumerable cases of bowel rupture the site of which varied from the ileum (Poelman³⁵) to every part of the colon (cecum,

28. Braun, cited by Koch: *Missbildungen von Verengerungen und Verschlüssen*, in Henke and Lubarsch (footnote 2, p. 189).

29. Farr, R. E., and Brunkow, C. W.: *Congenital Abnormalities of the Intestine*, Arch. Surg. **11**:417 (Sept.) 1925.

30. Chiari, cited by Sella (footnote 21).

31. Ciechanowski, S., and Glinski, L. K.: *Zur Frage der kongenitalen Dünndarmatresie*, Virchows Arch. f. path. Anat. **196**:168, 1909.

32. Cited by Rudnew (footnote 15).

33. Martens, S.: *Zur Kenntnis der Darmverschlüssen und Verengerungen*, Deutsche Ztschr. f. Chir. **57**:1, 1900.

34. Westphal, U.: *Kasuistischer Beitrag zur fötalen Peritonitis*, Monatschr. f. Geburtsh. u. Gynäk. **66**:245 (June 24) 1924.

35. Poelman, cited by Kuliga (footnote 20).

Dienst;³⁶ ascending colon, Pretty;³⁷ hepatic flexure, Bednar,³⁷ and descending colon, Lyss³⁷). Genital and urinary atresias are frequently associated with rectal anomalies. Without going any further into the complicated question of their origin, one may conclude that the peritonitis of such cases may be simply urinary, as in the case of abnormal communication of the bladder and uterus, or combined urinary and meconium in associated sigmoid rupture or fistula (Olshausen,³⁸ Sella²¹).

Cases without Obstruction.—I shall now consider those cases of meconium peritonitis without stenosis or atresia of the intestines. They form fully 50 per cent of all the cases of meconium peritonitis. An analysis of 23 cases shows that the perforations occur in the colon about twice as frequently as in the terminal ileum. The latter is the site of predilection in the small intestine, whereas all parts of the colon are equally involved. The causes of such perforations are manifold, and will be taken up in succession.

Trauma was considered of the utmost importance by Zillner.³⁹ He reported 4 cases of death from peritonitis from twelve to fifteen hours after delivery. In all these cases there was found a recent meconium peritonitis due to a perforation of the free border of the sigmoid through which the mucosa everted sleeve-like about the opening. Zillner³⁹ attributed the rupture to compression of the free sigmoid loop between the lumbar vertebrae and the anterior abdominal wall during labor. No microscopic studies were made, and a more definite conclusion, therefore, cannot be drawn. None of the numerous recent cases have been attributed to trauma.

Meconium stasis as a cause of rupture was first utilized by Paltauf.⁴⁰ Paltauf described spontaneous perforations of the colon and sigmoid in five new-born infants. These had all been spontaneous easy deliveries. Perforations occurred as widely gaping tears of the serosa and muscularis. Through these the submucosa and mucosa herniated, and were perforated in some places and remained intact in others. There were present, therefore, all stages of perforation, clearly indicating that the process started from without as a rupture of the outer two layers, with

36. Dienst, A.: Ueber Atresia Ani congenita, Virchows Arch. f. path. Anat. **154**:81, 1898.

37. Cited by Dienst (footnote 36).

38. Olshausen, R.: Zur Aetiologie der fötalen Peritonitis, Arch. f. Gynäk. **2**:280, 1871.

39. Zillner, E.: Ruptura flexurae Sigmoides Neonati interpartum, Virchows Arch. f. path. Anat. **96**:307, 1884.

40. Paltauf, A.: Die spontane Dickdarmruptur der Neugeborenen, Virchows Arch. f. path. Anat. **111**:461, 1888.

a subsequent herniation of the inner two and then a perforation of the latter. Microscopic examination revealed no ulceration of the mucosa. Serial studies showed the primary change to be an arterial compression, venous dilatation and necrosis of the muscularis at the site of rupture with much reactive infiltration and hemorrhage. Paltauf ascribed these changes to meconium stasis. The explanation of the stasis was not attempted. Hughes⁴¹ described a perforation of a stercoral ulcer in the transverse colon caused by a mass of meconium. Similar cases of meconium obstruction in the terminal ileum were contributed by Bullowa and Brennan,⁴² and Fanconi⁴³ and in the descending colon by Rudnew. A satisfactory explanation of these cases was not offered. Intestinal aplasia, faulty and deficient innervation of the bowel and hypersecretion or deficient secretion of the intestinal glands are some of the many theories. In only two cases were adequate explanations forthcoming.

Landsteiner,⁴⁴ in 1905, explained intestinal obstruction in a newborn infant on the basis of a putty-like column of meconium which was intimately adherent to the mucosa of the terminal ileum. The bowel above was hypertrophied, and the colon was empty and contracted. The pancreas showed extensive interstitial fibrosis and cellular infiltration. He concluded from the studies of Zweifel⁷ and Langendorff¹⁰ on fetal physiology that the absence of the pancreatic secretion in some way deprived the meconium of essential elements, probably enzymes, in addition to water, and the meconium thus became fatty and putty-like. Such a meconium was difficult to propulse and piled up in the ileocecal region. An almost identical case was recently contributed by Kornblith and Otani.⁴⁵ In their case, the pancreatic duct was stenosed and the putty-like meconium had caused ulceration of the ileum and a rupture of the ascending colon. It is worthy of note that an identical mass of putty-like adherent meconium caused obstruction in the terminal ileum in a case reported by Fanconi.⁴³ The pancreas in his case was normal, but the liver showed evidence of obstruction of the bile ducts due to an aplasia of the large ducts. Deprivation of bile can apparently produce a fatty meconium similar to that produced by deprivation of pancreatic secretion (similar to conditions in adults).

41. Hughes, E. E.: Acute Intestinal Obstruction Due to Inspissated Meconium, *Brit. J. Child. Dis.* **19**:32 (Jan.-March) 1922.

42. Bullowa, J. G., and Brennan, R. E.: Intra-Uterine Intestinal Obstruction from Inspissated and Impacted Meconium, *J. A. M. A.* **73**:1882 (Dec. 20) 1919.

43. Fanconi, G.: Fünf Fälle von angeborenen Darmverschluss, Dünndarmatresien, Duodenalstenose, Meconium Ileus, *Virchows Arch. f. path. Anat.* **229**: 207, 1921.

44. Landsteiner, K.: Darmverschluss durch eingedichtetes Meconium Pancreatitis, *Centralbl. f. allg. Path. u. path. Anat.* **16**:903 (Nov. 30) 1905.

45. Kornblith, B. A., and Otani, S.: Meconium Ileus with Congenital Stenosis of Main Pancreatic Duct, *Am. J. Path.* **5**:249 (May) 1929.

Fetal intestinal infections as a cause of intestinal perforations are obscure. Tolmatschew⁴⁶ described a meconium peritonitis in a 3 days old child produced by the perforation of a small gummatous ulcer. Cases of late fetal and intrapartum appendicitis were reported by Jackson⁴⁷ and Hill and Mason.⁴⁸ But a meconium peritonitis was not present.

Primary vascular insufficiency as a cause for bowel perforation was first advanced by Heibing⁴⁹ and supported by Spies.⁵⁰ This conception has been stressed by a number of authors as a cause for intestinal atresia (Wyss,⁵¹ Nobling,⁵² Jaboulay,⁵² and Davis and Poynter¹⁸). These vascular changes are no doubt secondary to the atresia, and Spies⁵⁰ offered proof in support of his conception. For his own case, he could not decide whether the condition was due to torsion of the intestine or fetal infection of maternal origin.

There is an important relation between congenital diverticula and meconium peritonitis. Meckel's diverticulum plays an important rôle in fetal obstructions and incarcerations. This has been reviewed by Halstead,⁵³ Porter,⁵⁴ Koch⁵⁵ and others. Meconium peritonitis due to a ruptured Meckel's diverticulum was described by Genersich⁵⁶ and Orth.⁵⁷ Recently Hunter⁵⁸ and Shukowski⁵⁹ reported gangrenous Meckel's diverticulum in new-born infants. The other congenital

46. Tolmatschew, cited by Peiser (footnote 1).

47. Jackson, W. F.: A Case of Prenatal Appendicitis, *Am. J. M. Sc.* **127**: 710, 1904.

48. Hill, W. B., and Mason, C. C.: Prenatal Appendicitis with Rupture and Death, *Am. J. Dis. Child.* **29**:86 (Jan.) 1925.

49. Helbing, T.: Ueber fötale Peritonitis nebst einem kasuistischen Beitrag, Inaug. Dissertation, Freiburg, 1908.

50. Spies, Paul: Ueber fötale Peritonitis, Inaug. Dissertation, Heidelberg, 1917.

51. Wyss, M. O.: Ueber kongenitale Duodenal-Atresien, *Beitr. z. klin. Chir.* **26**:631, 1900.

52. Cited by Sella (footnote 21).

53. Halstead, A. E.: Intestinal Obstruction from Meckel's Diverticulum, *Ann. Surg.* **35**:471 (Jan.-June) 1902.

54. Porter, M. F.: Abdominal Crises Caused by Meckel's Diverticulum, *J. A. M. A.* **45**:883 (Sept. 23) 1905.

55. Koch, W.: Magen und Darm-Missbildungen: III. Erhaltenbleiben embryonaler Anlagen, in Henke and Lubarsch (footnote 2, p. 175).

56. Genersich, A.: Bauchfellentzündung beim Neugeborenen infolge von Perforation des Ileums, *Virchows Arch. f. path. Anat.* **126**:485, 1891.

57. Orth, cited by Genersich (footnote 56).

58. Hunter, W. C.: Perforated Gangrenous Meckel's Diverticulum in a New Born Infant, *Am. J. Dis. Child.* **35**:438 (March) 1928.

59. Shukowski, cited by Hunter (footnote 58).

diverticula have been recently review by Evans,⁶⁰ who reported their presence in all parts of the intestine. There were, however, none which were associated with meconium peritonitis.

Acquired diverticula are of utmost importance in adult pathology. Although denied by some (Hartwell and Cecil⁶¹), such diverticula are almost always of the false type; that is, they consist from the onset of hernial protrusions of the mucosa through the other layers of the intestinal wall. As early as in 1869, Klebs⁶² emphasized their relation to the interruption of the muscularis produced by the entrance of the mesenteric vessels in the small intestine. He believed that traction on the vessels produced these mucosal herniations. Hansemann⁶³ described 400 diverticula into the mesentery of the small intestine of an old man and laid stress on the importance of pulsion. Graser⁶⁴ restudied the diverticula in the sigmoid and found the presence of microscopic herniations of the mucosa into the perivascular connective tissue sheaths. These patients were particularly chosen because of concurrent general venous or portal obstruction. He attributed great importance to intermittent dilatation of the veins in the production of large muscle gaps through which herniations could readily take place. This view was rejected by Sudsuki,⁶⁵ who found sigmoid diverticula more frequent in cases without than with venous obstruction. The general consensus (Telling and Gruner⁶⁶) is that pulsion by constipation and gas is effective in producing these herniations, between the mesenteric leaves in the small intestine and between the taenia mesenterica and the two anterior free taenia in the colon (Drummond⁶⁷).

The age at which these sacculi occur is usually late. But they have been reported to occur as early as at the age of 7 (Aschhurst⁶⁸).

60. Evans, A.: Developmental Enterogenous Cysts and Diverticula, *Brit. J. Surg.* **17**:34 (July) 1929.

61. Hartwell, J. A., and Cecil, R. L.: Intestinal Diverticula; a Pathological and Clinical Study, *Am. J. M. Sc.* **140**:174 (July-Dec.) 1910.

62. Klebs, cited by Hartwell and Cecil (footnote 61).

63. Hansemann, V.: Ueber die Entstehung falscher Darmdivertikel, *Virchows Arch. f. path. Anat.* **144**:400, 1896.

64. Graser, E.: Ueber multiple falsche Darmdivertikel in der flexura Sigmoidea, *München. med. Wchnschr.* **46**:721 (May) 1899.

65. Sudsuki, K.: Ueber Divertikel am S. Romanum, *Arch. f. klin. Chir.* **61**:708, 1900.

66. Telling, W. H. M., and Gruner, O. C.: Acquired Diverticula, Diverticulitis and Peri-Diverticulitis of the Large Intestine, *British. J. Surg.* **4**:468, 1916-1917.

67. Drummond, H.: Sacculi of the Large Intestine with Special Reference to Their Relations to the Blood Vessels of the Bowel Wall, *Brit. J. Surg.* **4**:407, 1916-1917.

68. Aschhurst, cited by Hartwell and Cecil (footnote 61).

Diverticula of this character are important from their frequency of perforation. Peritonitis is not a rare complication. But that such diverticula or sacculi can occur in the fetus and by rupturing produce meconium peritonitis was first brought out by Rudnew,¹⁵ who described 2 cases of meconium peritonitis. His first case concerned a stillborn fetus of 6 months, showing a well calcified fetal peritonitis and a focal necrosis of the antimesenteric portion of the ileum, 21 cm. from the ileocecal valve and just above a sharp end in the bowel. The ileum above was dilated, the ileum below contracted. As the cause of the necrosis, he found two mucosal herniations into the mesentery. These had ruptured, and the escaped meconium had compressed the vessels. The increased intra-intestinal pressure had produced the mesenteric herniations. His second case concerned a full term infant that died on the fourth day. There was free meconium in the peritoneal cavity issuing from a perforation in the middle of the transverse colon. The splenic flexure, descending colon and sigmoid were distended and thinned by a large amount of meconium. The transverse and ascending colon were hypertrophic but contracted. The site of perforation was seen microscopically as a ruptured mucosal herniation. Further sections showed muscular gaps produced by vessels entering into the bowel, which were as much as 10 mm. in diameter. The vessels were so dilated as to appear cavernous. Rudnew,¹⁵ like Graser,⁶⁴ demonstrated early stages of diverticulum formation as mucosal herniations into the perivascular spaces. The actual herniation was produced through increased intracolonic pressure, as shown by the hypertrophy of the muscle of the transverse colon. No actual obstruction was present, and Rudnew¹⁵ assumed faulty innervation of the descending colon. He also concluded that the excessive development of the vessels had produced abnormally large gaps in the muscularis through which mucosal herniations readily took place. He further demonstrated similar but smaller muscle gaps in his first case.

Rudnew's¹⁵ cases parallel the adult condition perfectly, showing herniations at the mesenteric site in the small intestine and antero-laterally in the large intestine. Recently, Fischer⁶⁹ reported an identical case of ruptured diverticulum in the transverse colon and described similar muscle gaps in the colon. Kornblith and Otani⁴⁵ found the gaps produced by the entering vessels to be as wide as the whole muscle wall itself.

Antimesenteric herniations can also take place in the small intestine. Froboese⁷⁰ described three cases of meconium peritonitis due to pin-

69. Fischer, A. E.: Case of Fetal Peritonitis Following Spontaneous Rupture of the Large Intestine, *Am. J. Dis. Child.* **36**:774 (Oct.) 1928.

70. Froboese, C.: Ursache der fötalen Peritonitis (Meconiumperitonitis), *Virchows Arch. f. path. Anat.* **269**:595, 1928.

point perforations of the antimesenteric border of the lower ileum. In one of these cases, he observed wide muscle gaps and accepted Rudnew's¹⁵ conception. It is to be noted, however, that increased pulsion is the important factor in the production of these diverticula, and in the cases of Froboese⁷⁰ no form of obstruction was present and no evidence for increased intra-intestinal pressure which could produce these herniations. He admitted that he found nothing in his first two cases, and only muscle gaps (a normal occurrence) in his third case. Histologic data on the conditions at the site of perforation are not given. Finally, von Sury,⁷¹ in attempting to explain a case of meconium peritonitis resulting from a ruptured rectum, came to the conclusion that local aplasia was the only acceptable explanation, since, in his opinion, meconium stasis alone did not suffice to cause rupture. No histologic studies of the site of perforation were made.

Of the numerous causes for intestinal perforation in the fetus and the new-born infant reviewed in this article, not a single one seems adequate for my case. There was no form of obstruction and the muscularis above the perforation was not hypertrophic. The pelvic organs were normal. There was also no stasis of meconium; the latter was not abnormal in amount, consistency or distribution. The other organs were normal. There was no indication of syphilis. The Wassermann reaction of the blood was negative and the Levaditi stains were negative.

The vessels supplying the segment of perforated bowel were patent and normal. Neither Meckel's diverticulum nor the congenital diverticula described by Evans⁶⁰ were present. The possibilities of fetal enteritis and focal aplasia will be discussed later.

As previously mentioned, the essential observations at the sites of perforation were excessive development of lymphatic tissue, deeply penetrating intranodular crypts of Lieberkühn which rested on the muscularis, circumscribed disappearance of the longitudinal muscle layer with marked thinning of the circular layer, cystic dilatation of the glands of the reflected portions of the bowel and intra-lymphatic glandular proliferations in the segment of bowel immediately below the perforations.

I believe that the glands invading the lymphatic tissue and the excessive lymphatic tissue are of utmost importance in the explanation of the present case. Lauche⁷² recently extensively reviewed these intranodular gland proliferations. In addition to their occurrence as a

71. Von Sury, K.: Die spontane Darmruptur bei Neugeborenen, *Vrtljschr. f. gerichtl. Med.* **2**:91, 1912.

72. Lauche, A.: Die Heterotopien des Ortsgehörigen Epithels im Bereich des Verdauungskanaals, *Virchows Arch. f. path. Anat.* **252**:39, 1924.

sequel of ulcerative processes anywhere within the gastro-intestinal tract (Löhlein,⁷³ Konjetzny⁷⁴), comparative and embryologic studies have established them as not infrequently of normal occurrence. Lauche⁷² traced the origin of these glandular proliferations to the anti-mesenteric diverticula in 5 to 32 mm. embryos described by Lewis and Thyng.⁷⁵ From the available literature, he described their constant normal presence in *Echidna* (Klaatsch⁷⁶), their occasional occurrence in a wide range of mammals, in full-term fetuses and young children (Meyer⁷⁷) and in the appendix (Lubarsch⁷⁸) and colon (Orth⁷⁹) of adults.

Lauche believes these intralymphatic submucosal gland proliferations to be due to the breaking up of the muscularis mucosa by the lymphatic nodules. But if one is to accept his view that these penetrating glands are derived from the diverticula described by Lewis and Thyng⁷⁵ as occurring in 5 to 32 mm. embryos, their development precedes that of the lymphatic tissue by a long period, since the latter develops in the embryo at 240 to 300 mm.

I therefore explain the excessive lymphatic tissue as a response to the abnormal persistence of these diverticula just as occurs when the invasion is secondary to an ulcerative process. The observations in my own case justify this conception. Both at the site of perforation and below it, the glands penetrate deeply and are surrounded by excessive amounts of lymphatic tissue. The circumscribed disappearance of the longitudinal muscle fibers and the marked thinning of the circular layer are probably the result of pressure from the large accumulation of lymphatic tissue. The changes at the second small perforation show clearly the disappearance of the muscle tissue and at the large perforation how excessively the lymphoid tissue may develop. These areas of diminished strength then ruptured and permitted the exit of meconium. The perforation probably occurred as the rupture of a deeply penetrating gland.

73. Löhlein, cited by Lauche (footnote 72).

74. Konjetzny, A. I.: Ueber die Beziehungen der chronischen Gastritis mit ihren Folge-erscheinungen und des chronischen Magenulcus zur Entwicklung des Magenkrebses, Beitr. z. klin. Chir. **85**:455, 1913.

75. Lewis, F. T., and Thyng, F. W.: The Regular Occurrence of Intestinal Diverticula in Embryos of Pig, Rabbit and Man, Am. J. Anat. **7**:505, 1907-1908.

76. Klaatsch, cited by Lauche (footnote 72).

77. Meyer, R., in discussion of Lubarsch, O.: Ueber heterotope Epithelwucherungen und Krebs, Verhandl. d. deutsch. path. Gesellsch. **10**:216, 1906.

78. Lubarsch, cited by Lauche (footnote 72).

79. Orth, J.: Ueber die Beziehungen der Lieberkühn'schen Krypten zu den Lymphknötchen des Darms unter normalen und pathologischen Verhältnissen, Verhandl. d. deutsch. path. Gesellsch. **3**:135, 1901.

The cystic character of the glands in the portion of mucosa reflected about the perforation is probably secondary to the inflammatory processes in the peritoneum to which the glands were exposed and not to a primary enteritis, for which there is no proof. To speak of local aplasia of the muscularis is too indefinite.

Although histologic studies of intestinal perforations are few, there are none on record in which observations similar to mine have been made. Whether, therefore, the latter are unique or whether further study will reveal them as of more common occurrence remains to be seen.

SUMMARY

A case of meconium peritonitis due to a perforation in the lower ileum is reported. At the site of perforation were: excessive development of lymphatic tissue, deeply penetrating crypts of Lieberkühn which rested directly on the muscularis and a local sharply circumscribed absence of the longitudinal muscular layer, marked thinning of the circular muscular layer and cystic dilatation of the glands of the mucosa reflected about the perforation. Below the perforation was a large amount of lymphatic tissue with deeply penetrating crypts of Lieberkühn, which here also rested directly on the muscularis.

The sequel of events is conceived to be primarily a persistence of fetal antimesenteric diverticula. In response to these, excessive lymphatic tissue developed, which caused pressure atrophy of the muscularis. Peristalsis ruptured this local area of diminished resistance. The cystic character of the glands is attributed to the inflammatory processes in the peritoneum.

The literature is reviewed with reference to the etiology of meconium peritonitis.

A COMPARISON OF CERTAIN INTRANUCLEAR INCLUSIONS FOUND IN THE LIVERS OF DOGS WITHOUT HISTORY OF INFECTION WITH INTRANUCLEAR INCLUSIONS CHARACTERISTIC OF THE ACTION OF FILTRABLE VIRUSES *

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In connection with the study of intranuclear inclusions produced in the hepatic cells of man and monkeys by the virus of yellow fever (Cowdry and Kitchen¹), many other hepatic lesions were examined for purposes of control. Among these were many preparations, and blocks of tissue which we sectioned and stained for ourselves, from the livers of dogs kindly given to us by Dr. Otto Schwarz and Dr. W. J. Dieckmann. The dogs had been employed in experiments designed to produce lesions like those characteristic of human cases of eclampsia (Dieckmann²). What interested us particularly was the discovery in some of them of what seemed to be typical intranuclear inclusions. Indeed, the bodies were so like those formed in virus diseases as to raise the question of whether a virus was not actually at work in the tissues.

A detailed study of these inclusions promised to yield interesting results; for, if it should be shown that the inclusions were in fact a manifestation of virus action, the possibility that they were caused by a virus not hitherto recognized would have to be tested. Thus far, viruses affecting by preference endodermal cells, particularly the cells of the liver, are rare. We know of only one, namely, that of yellow fever. The discovery of another in a common laboratory animal would afford valuable opportunities for experimentation. Conversely, if it should be ascertained that the inclusions merely result from the experimental conditions imposed on the liver, the condition would be still more interesting. It would constitute the only known case of such

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1. Cowdry, E. V., and Kitchen, S. F.: Intranuclear Inclusions in Yellow Fever, *Science* **69**:252, 1929.

2. Dieckmann, W. J.: The Hepatic Lesion in Eclampsia, *Am. J. Obst. & Gynec.* **17**:454, 1929; Further Observations on the Hepatic Lesion in Eclampsia, *Am. J. Obst. & Gynec.* **18**:757, 1929.

intranuclear inclusions being found in the absence of virus and would act as a corrective against the prevalent conception, which at present has everything in its favor, that inclusions of this general type point rather clearly to the action of a virus.

Obviously, the first step was to determine just how close the resemblance actually is between these as yet unknown inclusions in dogs and others which have definitely been proved to be caused by filtrable and as yet ultravisible agents in other tissues. Our results in this direction are presented in this paper and the likelihood of the presence of a hitherto unrecognized filtrable virus is discussed.

INCIDENCE OF THE INCLUSIONS

The livers of sixty-eight dogs were available for examination. The general course of treatment in all of them was to give "a full meal of raw meat daily followed by the injection of tissue fibrinogen or lung extract in the general circulation 1 hour later; the dosage varied from 0.5 to 3 cc. of tissue fibrinogen or lung extract. Frequently, after the injection into the general circulation, the animal would cry out, urinate, have evacuations from the bowels and develop convulsions. The animals were sacrificed at varying periods of from two to seven days; they were always sacrificed when the symptoms produced by the injections were marked, so as not to have the animal die during the night" (Dieckmann³).

Careful study revealed typical intranuclear inclusions in only two, which means that their incidence is lower than was at first supposed. The history of these dogs is as follows:

Dog 67, male, weighing 6,250 Gm., was fed raw meat on March 26, 1929. One hour later, the animal was given 1 cc. of a saline extract of ground up calf lung by intracardiac injection. The dog voided, showed some signs of shock and died three hours later.

Dog 36, female, weighing 6,810 Gm., was fed regularly on a diet of raw meat and given daily injections of fibrinogen for nine days beginning with 1.5 cc. and gradually increasing to 3 cc. The dog died two hours after the ninth dose.

There is no reason to suppose that they were treated differently from the others, except, perhaps, in respect to details which would not seem to be the controlling factors and which were so insignificant as to escape mention in the protocols. To check this possibility; we tried to secure other livers laden with intranuclear inclusions by duplicating the experimental procedures. In this and all our other experiments, ether was used as an anesthetic. Five futile attempts left us with the impression that the intranuclear inclusions might not result from the experiments at all. We then made a comprehensive study of the lesions

3. Dieckmann (footnote 2, second reference).

in the livers containing the intranuclear inclusions to determine in just which respects they corresponded and differed from the large majority of the series.

The intranuclear inclusions were present in approximately 80 per cent of hepatic parenchymal cells and 20 per cent of endothelial cells in dog 67. In the other dog, the corresponding percentages were about 20 and 5. In both dogs, their presence was definitely associated with hemorrhage and necrosis in the central and middle thirds of the hepatic lobules and with an increase in the number of phagocytic cells, especially polymorphonuclears and macrophages. There was also rather marked swelling of the endothelium of the sinusoids. The livers of several other dogs, which were modified in much the same way, contained no intranuclear inclusions. Since, for this reason, the hypothesis seemed strengthened that the special experiments of Dieckmann might not be the determining influences in the production of the inclusions, the livers of still other dogs were examined to see whether the inclusions could be found in dogs which had not been made the subject of such experiments. These control livers were from several sources: four from dogs treated with carbon tetrachloride by Dr. Paul D. Lamson; four from dogs into which we had injected, intrahepatically, active herpetic virus in order to determine whether the inclusions under investigation looked like those characteristic of herpes, as will be mentioned later; eight from dogs into which had been injected, intrahepatically, ground up liver substance in series, as will be described subsequently, and three from dogs employed in various experiments by Dr. I. Y. Olch, which were also quite different from those of Dieckmann.

In none of these nineteen livers were any of the inclusions seen; but these negative observations were not sufficiently numerous to settle positively the question of whether the incidence of the inclusions was related to Dieckmann's experiments. No inclusions resembling them were observed in the livers of fifty monkeys experimentally infected with the virus of yellow fever or in the livers from fifty patients who had died from the disease.

Whether similar intranuclear inclusions occur in tissues other than the liver we cannot at present state, because only the liver with now and then a section of kidney and spleen was available from each dog for examination.

PROPERTIES OF THE INCLUSIONS

The inclusions presented the features usually exhibited by intranuclear inclusions in virus diseases. The livers from the two dogs with inclusions had been fixed in Kaiserling's fluid, which would not be likely to alter their subsequent tinctorial properties, but which was

not favorable for microchemical analyses. Like other intranuclear inclusions they were acidophilic, staining by preference with "acid" dyes, such as eosin, erythrosin and phloxin, so that they appeared red or pink in contrast with the blue-colored basophilic chromatin after staining with eosin-methylene blue, hematoxylin and eosin, Giemsa stain and other similar combinations.

Topographically, the intranuclear inclusions occupied the centers of the affected nuclei as may be seen by reference to figure 1. In field 1, an inclusion-laden nucleus in an hepatic cell is visible a little to the right of the center. The inclusion is dark and looks homogeneous. It is separated from the nuclear membrane by a characteristic area of rarefied nucleoplasm which is not stained. It can be seen, also, that the chromatin is irregularly margined on the nuclear membrane being rather more dense above and to the left.

In the center of field 2, an endothelial nucleus is represented, likewise carrying an inclusion, the morphology of which is molded after that of the limiting nuclear membrane. The surrounding clear area and the irregular margination of chromatin are well shown.

The lower view (3) shows three nuclei with typical inclusions, all in hepatic cells. The one to the left contains an almost spherical inclusion, the outlines of which are clearcut. The inclusion is excentrically placed. A little above and to the left of it, the nuclear membrane appears to be thickened, a change which is caused by the disintegrating nucleolus being closely applied to it. The other two nuclei are contained within a single hepatic cell and are to the right of the center of the figure. The outlines of the cell membrane can be roughly determined. One of these nuclei presents two inclusions, which is unusual. It will be observed, however, that the actual amount of inclusion material is approximately the same in the two nuclei. The outlines of the inclusions are not so sharp as in the case of those already mentioned. Delicate and tapering strands of substance seem to pass out from them across the clear area toward the nuclear membranes.

Inclusions in many stages of formation were always visible even in a single slide, though those which have been described predominated. With care, the seriation in changes could be made so complete that we can speak with confidence of a process taking place. On the one hand, there were presumably the early stages which seemed to be most numerous in the peripheral parts of the lobules. These were characterized by the accumulation in the central parts of the nuclei of minute acidophilic particles which became more and more tightly packed together until they fused into a single mass; at the same time, the nucleolus was displaced to one side, and the ground substance of

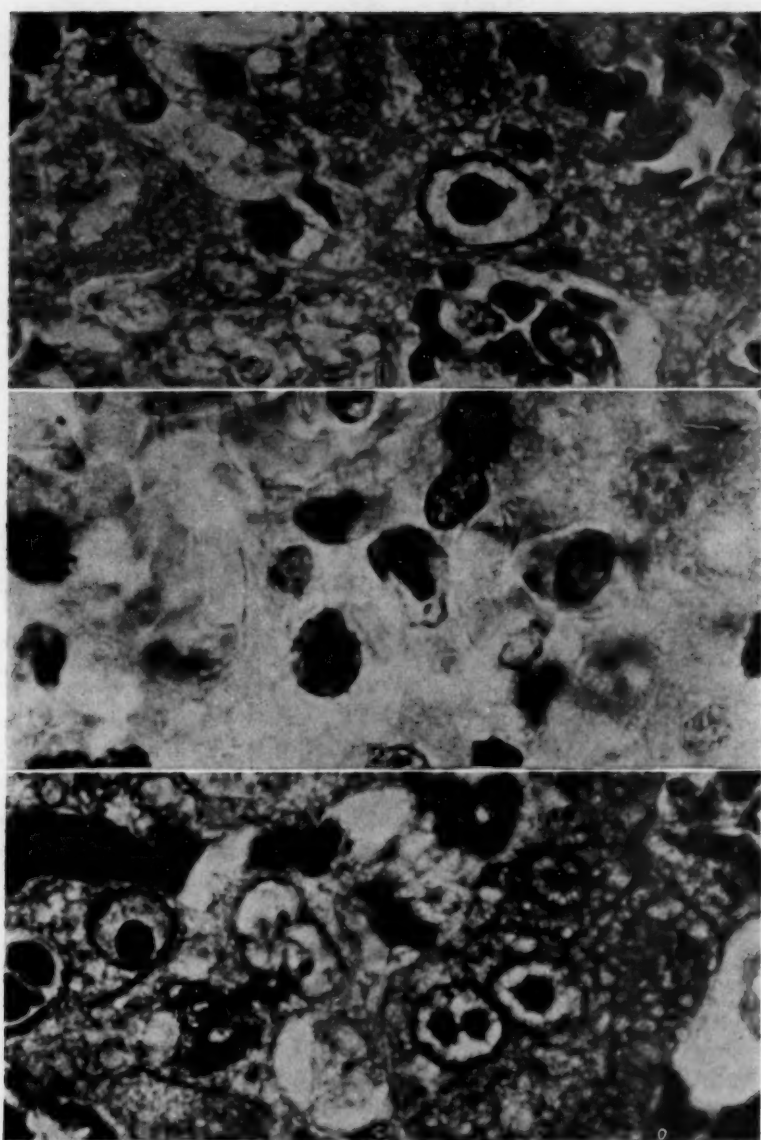


Fig. 1.—(1) A little to the right of the center, a nucleus of an hepatic cell is seen containing a well marked, centrally placed inclusion, which is separated from the nuclear membrane by a halo of relatively unstained nucleoplasm; $\times 1,200$.

(2) Almost in the middle of the photograph is an endothelial nucleus containing an inclusion the form of which corresponds rather closely to the shape of the nucleus itself. Basophilic chromatin is marginated irregularly on the nuclear membrane; $\times 1,200$.

(3) Several nuclei containing inclusions are shown. In the nucleus to the left, the inclusion is almost spherical and is excentrically placed, being in contact on one side with the nuclear membrane. Slightly lower and to the right are two nuclei in contact. One of these has a double inclusion and the other a single one. The outlines of the inclusions are more irregular with faint strandlike extensions of material toward the nuclear membrane; $\times 1,200$.

the nucleus became cleared of basophilic chromatin, which was condensed, with the remains of the nucleolus, on the surface of the nuclear membrane.

On the other hand, there were more advanced stages in the process, which by contrast were chiefly found in the central areas of the lobules. We have noted the fact that accompanying the inclusions there was a marked central necrosis. As the change in the nuclei proceeded beyond the stages represented in our photomicrographs, the inclusions enlarged further and the nuclei shrank slightly, so that a point was reached when the inclusions occupied almost the entire intranuclear space. Apparently, while this was happening, the basophilic chromatin, absorbed on the nuclear membrane, became still more irregular in disposition, being heaped up in some parts and wholly absent in others.

Finally the nuclear membrane disappeared, often by lysis, but occasionally by rhexis, and the acidophilic material making up the inclusion could be distinguished with difficulty in the necrotic cytoplasm, which had also undergone an acidophilic change. In the parts of the lobules in which necrosis was most marked there were many macrophages and polymorphonuclears, which probably helped to remove the debris.

It is to be noted that these inclusions were different and distinct from certain intranuclear crystals described by Szymonowicz and Macallum⁴ and illustrated by a figure from a "Preparation of Browicz," which they thought to consist of methemoglobin. We found these crystals, often abundantly, in 22 per cent of the dog livers examined; that is to say, both in Dieckmann's series and in our other animals. They were hexahedra or pentahedra and from two to three times as long as they were broad. The maximum length measured was 25 microns, the average being about 10 microns. Like the inclusions, they stained with eosin and other "acid" dyes and when not colored artificially were unpigmented. They were often surrounded by halos of clear nucleoplasm, and as they were formed, the basophilic chromatin, with the nucleolus, was displaced toward the nuclear membrane, but was not adsorbed irregularly on its surface. When they were cut through their long axis, the morphology of the inclusions and the stretching out of the nucleus were distinctive. It was only when cut in cross-section that, at first sight, they sometimes suggested inclusions caused by a filtrable virus. But in such cases, careful examination always revealed plane surfaces and angles, and the nuclei did not become necrotic.

4. Szymonowicz, L., and Macallum, J. B.: *Textbook of Histology*, Philadelphia and New York, Lea Brothers & Company, 1902.

COMPARISON OF THE INCLUSIONS WITH THOSE CAUSED
BY FILTRABLE VIRUSES

Since much work on virus diseases has been done in our laboratory, material was at hand sufficient for a direct comparison of the inclusions with those typical of yellow fever, herpes, chickenpox, Borna disease, submaxillary disease and virus III disease. As far as we could tell, there was no clearcut microchemical difference in the materials involved, so that our observations were chiefly morphologic and topographic.

There was no possibility of confusing the inclusions with those in the liver characteristic of yellow fever, with which we were primarily concerned. They were of a much denser consistency and they were not made up of discrete colony-like masses of particles separated from each other by stretches of clear nucleoplasm. Furthermore, as they developed the nucleoli were soon destroyed, whereas in yellow fever the nucleoli persist. In a paper by Cowdry and Kitchen,⁵ there is a series of photomicrographs of inclusions typical of yellow fever taken at a higher magnification than those which illustrate this paper. A comparison of the two will show how definite are the differences mentioned.

In the case of herpes, we first took some H. F. herpetic virus in a rabbit's brain which had been preserved in glycerin and passed it intracerebrally in the usual way into a second rabbit. This animal soon exhibited the classic symptoms of herpetic encephalitis, and from it we secured fresh virus, which we injected intrahepatically into two dogs. After forty-eight hours had elapsed, the dogs were chloroformed and fragments of livers from the sites of injection were prepared histologically, but no herpetic intranuclear inclusions were found. The experiment was repeated, fresh virus being again prepared from the glycerinated virus. This time it was injected intrahepatically into three dogs, and the tissues were removed for examination from two of them after seventy-two hours and from the third after eighty-four hours, but again no inclusions were seen.

We were consequently obliged to use as controls for the comparison, not the livers of dogs, but the livers of two rabbits and of one monkey (*Cebus hypoleucus*), into which in the study of intranuclear inclusions in yellow fever, the same herpetic virus had been successfully injected. We observed that the unknown inclusions in our dogs differed from these herpetic inclusions in structure. They were much denser, and we did not find a stage corresponding to the almost complete filling up of the nucleus with acidophilic particles of rather variable size seen in herpetic infections. The associated nuclear changes, however, had this in common that in both the nucleoli were early destroyed, and there was

5. Cowdry, E. V., and Kitchen, S. F.: Intranuclear Inclusions in Yellow Fever, *Am. J. Hyg.*, to be published.

a margination of basophilic chromatin. But this margination of chromatin was more marked in herpes. For other details, reference should be made to the photomicrographs of herpetic inclusions published by Goodpasture and Teague⁶ and by Goodpasture.⁷

The comparison with the inclusions in chickenpox is not so valuable for the reason that the affected cells were so different, liver cells as compared with cells of the skin. The inclusions differed in much the same way as they did from those in herpes, but it does not follow that if the condition which we are investigating is due to a filtrable virus, and further that if this virus can be induced to act on the skin, that the inclusions produced will exhibit the same points of resemblance and of difference; for the character of the inclusions in virus diseases is governed not only by the kind of virus, but also by the type of cell responding to it.

The inclusions were compared with those characteristic of Borna disease only as the latter were seen in the nuclei of nerve cells. The necessary material was kindly given to us by Dr. I. A. Galloway of the National Institute for Medical Research, London, England. Like the inclusions in Borna disease, the unknown inclusions in our dogs were rounded acidophilic bodies surrounded by a zone of rarefied nucleoplasm; but here the resemblance ended, for destruction of nucleoli and complete margination of basophilic chromatin were not to be observed in Borna disease (Nicolau, Dimancesco-Nicolau and Galloway⁸).

The inclusions in dogs were much smaller than those produced by the submaxillary virus in the duct cells of the submaxillary gland, and rather larger than the inclusions which resulted when the same submaxillary virus was injected into the brain. In the former situation, the submaxillary inclusions were less dense, but in the latter they seemed to be of about the same density as the inclusions which we are studying in dogs. Photomicrographs of the submaxillary inclusions taken with the same optical combination yielding a magnification of 2,000 diameters will be available for comparison in a paper by Pearson.⁹

6. Goodpasture, E. W., and Teague, O.: Experimental Production of Herpetic Lesions in Organs and Tissues of the Rabbit, *J. M. Research* **44**:121 (plate 44, figs. 3-7) 1923.

7. Goodpasture, E. W.: The Axis-Cylinders of Peripheral Nerves as Portals of Entry to the Central System for the Virus of Herpes Simplex in Experimentally Infected Rabbits, *Am. J. Path.* **1**:11 (plate 3, figs. 1-3) 1925.

8. Nicolau, S.; Dimancesco-Nicolau, O., and Galloway, I. A.: Étude sur les septénévrites à ultra virus neurotropes, *Ann. de l'Inst. Pasteur* **43**:1 (plate 1, fig. 1) 1929.

9. Pearson, E. F.: Cytoplasmic Inclusions Produced by the Submaxillary Virus, to be published (figs. 1 to 3).

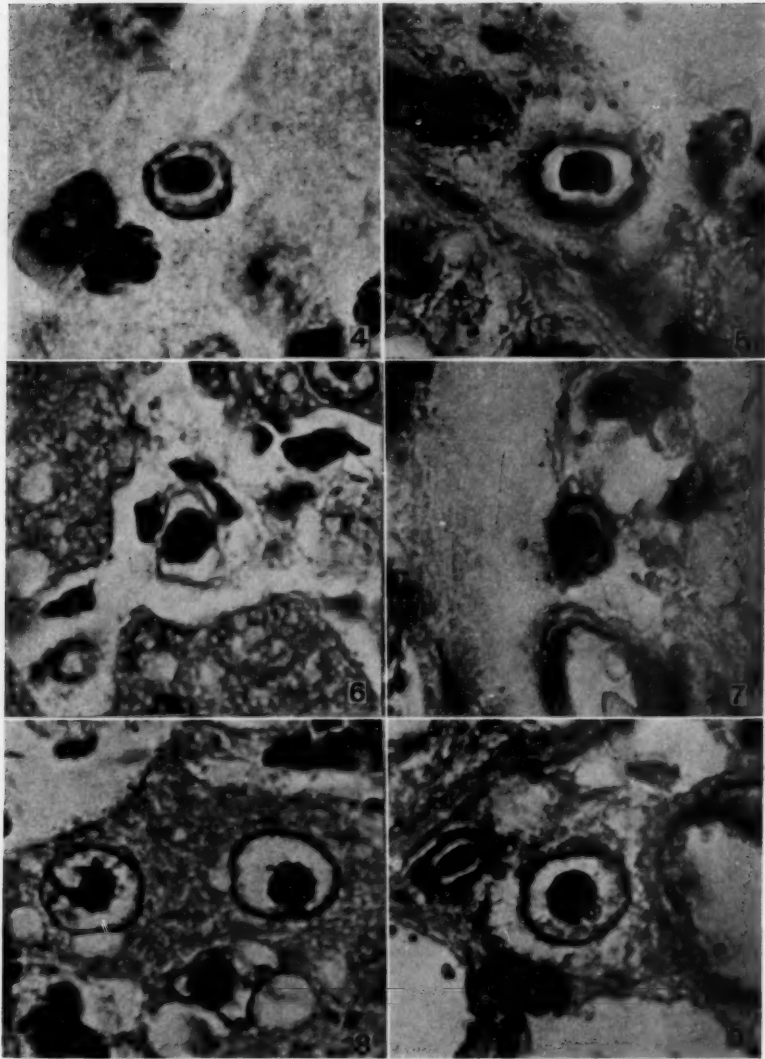


Fig. 2.—The three fields on the left are photomicrographs of intranuclear inclusions in the liver cells of dogs (nos. 36 and 67), $\times 1,200$; those on the right are also photomicrographs but of inclusions caused by virus III in the testicles of rabbits taken at a higher magnification of 1,600 diameters. The similarity between the inclusions in dogs and those in the virus III infection is evident.

But when we came to the inclusions produced by virus III in the testicle, the correspondence was remarkably close. Figure 2 has been prepared in order that it may be accurately gaged. The fields are arranged in two columns. To the left are three photomicrographs (4, 6 and 8) of the questionable inclusions in the livers of dogs; while to the right are three other photomicrographs (5, 7 and 9) of the inclusions produced by virus III in the testicles of rabbits, which were unfortunately taken at a higher magnification, which as the figures are reproduced amounts to 1,600 diameters instead of 1,200. In this way, provision is made for three comparisons.

In the first pair, an inclusion is represented in the nucleus of a hepatic cell of a dog (4) and another in a cell inhabiting the interstitial tissue between the seminiferous tubules of the rabbit's testicle (5). It will be noted that the inclusions are of about the same size and approximately of the same density, though the virus III inclusion is a little darker in the photomicrograph. The clear area between the centrally placed inclusion and the nuclear membrane is less marked in the liver cell than in the other. There is a margination of chromatin on the nuclear membrane in both, but it is more extensive in the case of the nucleus injured by virus III.

The second pair of fields (i. e., 6 and 7) illustrates also a close degree of correspondence. Both represent intranuclear inclusions in endothelial cells. Here, again, the inclusion caused by virus III (7) appears to be rather more dense, but this, we think, is not significant. It may be due to differences in exposure and in printing in making the photomicrographs, for corresponding differences were not observed in the actual study of the specimens. The clear area between the inclusion and the nuclear membrane is relatively more extensive in the case of the unknown inclusion (6), and the margination of chromatin is less noticeable.

In the third and last pair of fields, namely, 8 and 9, several affected nuclei are represented, three in hepatic cells of the dog's liver and two in the rabbit's testicle. The smaller of these two is an endothelial nucleus and the larger is the nucleus of an interstitial cell. The similarity of the inclusions is obvious and does not require detailed mention.

If it were not for the fact that liver cells are involved in one instance and the cells of the testicle in the other, we believe that it would be impossible to distinguish between the inclusions. It may be added that the nuclear changes shown in a photomicrograph of Rivers and Tillett¹⁰ are likewise indistinguishable from those seen in our two dog livers.

10. Rivers, T. M., and Tillett, W. S.: Further Observations on the Phenomena Encountered in Attempting to Transmit Varicella to Rabbits, *J. Exper. Med.* **39**:777 (fig. 2) 1924; The Lesions in Rabbits Experimentally Infected by a Virus Encountered in the Attempted Transmission of Varicella, *ibid.* **40**:281, 1924.

Having in mind the methods by which Rivers and Tillett concentrated and established virus III in the testicles of rabbits, we made corresponding experiments with dogs. They stated that it was only after four consecutive passages of ground up testicle substance that distinctive lesions were produced containing the intranuclear inclusions, and, further, that an interval of from three to six days was allowed to elapse after each intratesticular inoculation before the inoculated testicles were removed and ground up in saline solution for the inoculation next in series.

Accordingly, with aseptic precautions we removed a fragment of liver from an apparently normal dog and made from it a 10 per cent emulsion in physiologic solution of sodium chloride. A small opening was made in the abdominal wall of a second dog which was under ether anesthesia, and 10 cc. of the emulsion was injected by a hypodermic syringe into the liver substance at a depth of about 1 cm. from the surface in selected areas which could be accurately located again later, both to the right and to the left of the anterior median fissure. After four days had elapsed, during which the dog showed no untoward symptoms, tissue was removed from the sites of injection. Some of it was preserved for histologic examination, and the remainder was emulsified and passed to a third dog in the same manner. This third dog remained apparently normal. After four days, passage was made from the third to a fourth dog, which died twenty-four hours later from severe peritonitis and septicemia. The emulsion made from tissue from the areas of injection in this animal was consequently filtered through a Berkefeld N candle, and the filtrate was injected intrahepatically into a fifth dog. This fifth dog exhibited no resulting clinical symptoms and was chloroformed likewise on the fourth day. Unfiltered emulsion was then passed to a sixth dog, which also remained apparently normal. After the same period of four days, the hepatic emulsion made from its liver was injected intrahepatically into a seventh and an eighth dog, and a Berkefeld filtrate of the same emulsion was made and injected into the right testicles of two rabbits. The seventh dog was chloroformed after two days and the eighth dog after six days. Neither showed any intranuclear inclusions. Both rabbits were killed forty-eight hours after inoculation, and in their testicles also we failed to find any intranuclear inclusions. Inclusions were also absent in all of the intervening transfer animals. This means that our efforts by repeated passage to establish the virus, if any, responsible for the development of the inclusions were unsuccessful.

There is no known filtrable virus disease in dogs of which these inclusions, so closely resembling those of virus III, are likely to be the expression. The inclusions which have been described by many investigators in canine distemper are cytoplasmic and are generally restricted

to the cells of the central nervous system, though some have been reported by Babes and Starcovici¹¹ in the bronchial and alveolar epithelial cells as well. Orel and Silberstein¹² presented evidence that in a certain number of dogs a filtrable virus exists in the nasal passages, which on corneal, subdural and endolumbar inoculation causes death in both dogs and rabbits, but they said nothing of the occurrence of intranuclear inclusions. We have not as yet made a search for this virus.

COMMENT

It is improbable that the inclusions which we have described in the livers of these two dogs were merely the result of the histologic technic employed, because the same technic was used in the case of many other dogs without bringing them to light, and because repeated attempts by numerous workers to produce inclusions experimentally have failed. It is also unlikely that they resulted from the experiments performed by Dieckmann, for they have made their appearance in only two of the sixty-eight dogs examined, and also because we repeated the treatment accorded to these two dogs just as accurately as we could in the case of five others without producing any inclusions. Our series of dogs, which were not included in Dieckmann's experiments, is by comparison a small one, amounting to only sixteen, but in these no inclusions were seen. It is possible that if this series were extended to an equal number of animals, others showing intranuclear inclusions would be discovered.

The tendency now is to regard the presence of such inclusions as indicative of the action of a filtrable virus. Cole and Kuttner,¹³ for instance, espoused this interpretation definitely. After many attempts to produce intranuclear inclusions by other means than the injection of filtrable viruses had proved unsuccessful, they summed up by saying: "It is true that Luger and Lauda have mentioned the occurrence of similar structures in a case of salvarsan dermatitis. Even though these lesions should be present in isolated instances of this kind, it would be necessary to demonstrate the absence of a filterable virus in the given instance before the present conception of the direct relationship between these nuclear changes and filterable viruses would become untenable." In other words, these investigators believed that when typical intra-

11. Babes, V., and Starcovici, C.: Sur les corpuscles particulieres trouvés dans la maladie des jeunes chiens, *Compt. rend. Soc. de biol.* **73**:229, 1912.

12. Orel, H., and Silberstein, F.: Experimentelle Encephalitisstudien: IV. Ueber das Vorkommen von Encephalitisvirus im Nasenrachenraum gesunder Hunde, *Ztschr. f. d. ges. exper. Med.* **44**:280, 1925.

13. Cole, R., and Kuttner, A. G.: A Filterable Virus Present in the Submaxillary Glands of Guinea-Pigs, *J. Exper. Med.* **44**:855, 1926.

nuclear inclusions are found, the presence of a filtrable virus is to be assumed, unless its absence can be proved experimentally.

While we hesitate to subscribe without reservation to the point of view expressed by Cole and Kuttner, we do feel that our observation of intranuclear inclusions in these two dogs is on a par with the occasional discovery of intranuclear inclusions in a small percentage of human beings, particularly in infants, in the absence of distinctive clinical symptoms (Goodpasture and Talbot,¹⁴ Wilson and DuBois,¹⁵ Von Glahn and Pappenheimer¹⁶ and others). There is this difference, however, that the possibility of experimentation in dogs holds out greater hope for an understanding of the problem than the study of human tissues, which must always be largely opportunistic.

CONCLUSION

Intranuclear inclusions were found abundantly in the hepatic cells and endothelial cells of two dogs in association with centrally placed necrotic changes in the lobules. The further observation that these intranuclear inclusions are indistinguishable from the inclusions which are produced in the testicles of rabbits by the action of virus III indicates the possibility that a hitherto unrecognized filtrable virus may occur in a small percentage of these common laboratory animals.

14. Goodpasture, E. W., and Talbot, F. B.: Concerning the Nature of "Protozoan-Like" Cells in Certain Lesions of Infancy, *Am. J. Dis. Child.* **21**:415 (May) 1921.

15. Wilson, J. R., and DuBois, R. O.: Report of a Fatal Case of Keratomalacia in an Infant, with Postmortem Examination, *Am. J. Dis. Child* **26**:431 (Nov.) 1923.

16. Von Glahn, W. C., and Pappenheimer, A. M.: Intranuclear Inclusions in Visceral Disease, *Am. J. Path.* **1**:445, 1925.

THE EFFECT OF INTRAVENOUS INJECTION OF DEXTROSE ON THE KUPFFER CELLS OF THE LIVER *

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In the course of our studies on the value of injections of dextrose in the postoperative state, histologic examination of the liver was performed as a routine procedure. In a series of twenty-seven cases in which upper abdominal operations were done, the patients were subjected to excisions of two wedge-shaped pieces of liver. One section was removed immediately before and another half an hour after the intravenous administration of 250 cc. of 20 per cent dextrose solution. Some of these patients received an injection of either 5 cc. of a solution of trypan blue or 5 cc. of Higgins' india ink into the left gastro-epiploic vein. These injections of dye were given for the purpose of vital staining the reticulo-endothelial cells of the liver in order more easily to visualize any possible change in them.

The order of the steps in our experiment can be summarized as follows: Under spinal anesthesia an upper right rectus incision was made. The dye for vital staining was then injected. The first excision of liver tissue followed. Immediately afterward dextrose was injected intravenously into a vein of the antecubital fossa. The operation was then performed, and half an hour after the injection of dextrose a second piece of liver was removed. The control experiment consisted of the substitution of 250 cc. of physiologic solution of sodium chloride for dextrose. The sections of liver were fixed in formaldehyde, and frozen as well as paraffin sections were made. The sections were studied partly unstained and partly after application of the usual staining methods.

HISTOLOGIC DESCRIPTION

In normal human liver, if proper staining is employed, the nuclei of the Kupffer cells stand out fairly well because of their intense absorption of hematoxylin. It is true that in some of these cells the nuclei are larger and are only fairly stained. The majority, however, appear as elongated and more or less spindle-shaped or rod-shaped

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* From the Departments of Surgery and Pathology, Crown Heights Hospital.

nuclei perfectly parallel to the capillary wall. After the injection of dextrose most of the nuclei change their appearance and become larger and oval and show a much less dense distribution of their chromatin. In consequence of these changes, the staining with hematoxylin is much lighter. These nuclear changes are accompanied by swelling of the cytoplasm, which seems to detach itself more from the capillary wall. It also seems that the cytoplasm of these cells, after the injection of dextrose, stains more intensely and assumes a somewhat bluish shade. This would indicate a certain basophilia of the cytoplasm, or a change in the pH toward the acid side.

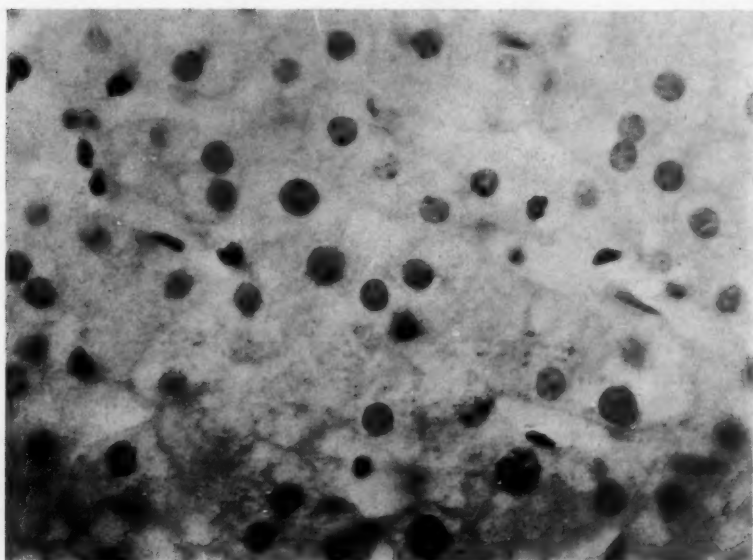


Fig. 1.—Section of the liver before the injection of dextrose. Note the dark rod-shaped nuclei of the Kupffer cells.

The changes described, although definite, are so minute that they might be overlooked by the less attentive observer. If, however, vital staining is employed previous to the injection of dextrose, the changes are much more conspicuous. While the faintly stained cytoplasm of the Kupffer cells is not easy to observe, the presence of trypan blue and particularly of india ink demonstrates strikingly the swelling of the cell bodies. These larger cells, however, seem to ingest more of the dye-stuff than they would take in before the administration of dextrose. In other words, it seems that they are more effective phagocytes after than before the injection of dextrose.

The histologic observations can be summarized as follows: The injection of dextrose elicits morphologic changes in the Kupffer cells

which consist of swelling of the cell body and nucleus; changes also occur in the chromatin distribution and in the staining properties of the cytoplasm. These changes are observed readily in the Kupffer cells without the vital staining. They were much more conspicuous when vital staining was employed, particularly in the cases in which india ink was used. But it also seems that the phagocytosis of the Kupffer cells for the dye is enhanced by the stimulation which the cell has apparently received by experimental procedure.

Swelling of a cell and its nucleus with concomitant changes in the chromatin distribution of the latter is looked on as an expression of

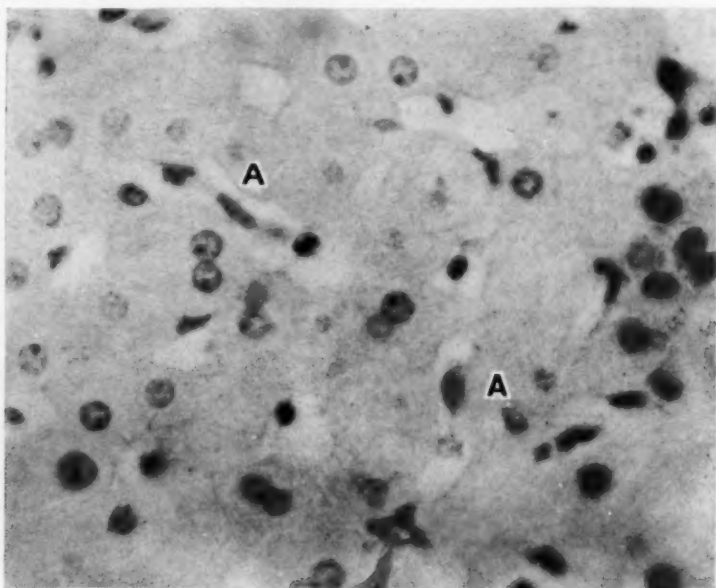


Fig. 2.—Section of the liver from the same patient after the injection of dextrose. Note the larger, paler nuclei and the swollen cytoplasm of the Kupffer cells at *A*.

increased function of that particular cell. The changes described in the Kupffer cells justify the opinion that they have been stimulated to increased activity. The stimulating factor is undoubtedly the dextrose solution. This has been ascertained by the control which includes cases in which injections of dextrose were made without previous vital staining and cases in which vital staining was employed but physiologic solution of sodium chloride substituted for dextrose. In the control experiments, these changes were observed in the former but not in the latter set. This would indicate definitely that the dextrose alone was responsible for the changes in the cells.

We realize that the changes produced by the injection of dextrose are not specific; they are similar to changes that occur after the injection of protein bodies, metal salts and hormones. In all of these instances, however, their significance is similar. They indicate increased functional activity. The Kupffer cells of the liver form part of the reticulo-endothelial system, the manifold function of which includes defense of the organism against infection and participation in intermediary metabolism. Stimulation of the reticulo-endothelial cells is expected to increase the resistance against infection and to facilitate the course of metabolic processes.

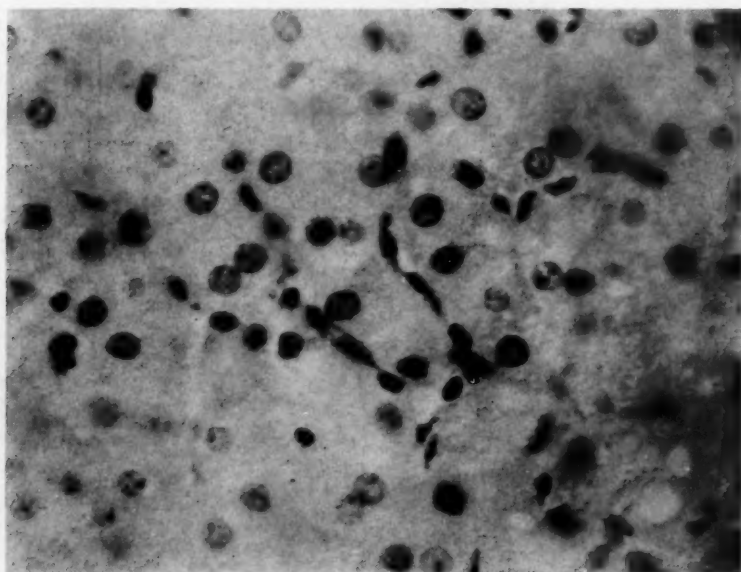


Fig. 3.—Section of the liver stained vitally with india ink.

The intravenous injection of dextrose has been found of considerable clinical value in many conditions. In the postoperative state complicated by infection or shock it is our experience that dextrose has a distinct value. It is helpful in overcoming the severity of the infection; it combats shock and favors smoother convalescence. Similar experiences are universally reported, and the administration of dextrose has become a generally accepted therapeutic procedure.

Schoenig,¹ in a study of the effect of massive doses of the roentgen rays in malignant conditions, demonstrated an inability on the part of the reticulo-endothelial cells to store vital dyes during the period of

1. Schoenig: *Klin. Wchnschr.* 8:651, 1929.

roentgen "shock." This disability of the cells was found in direct proportion to the severity of the clinical symptoms of "shock." Schoenig believed that the injury to the reticulo-endothelial cells by irradiation resulted in their inability to dispose adequately of protein cleavage products which were formed by the roentgen exposure. The value of intravenous injections of dextrose in the treatment for roentgen shock, as advised by Mayer² and others, could be ascribed to a stimulatory effect on the reticulo-endothelial cells as a result of which they could resume their physiologic functions and dispose of the toxic elements. Such stimulation would be analogous to that shown in our experiments.

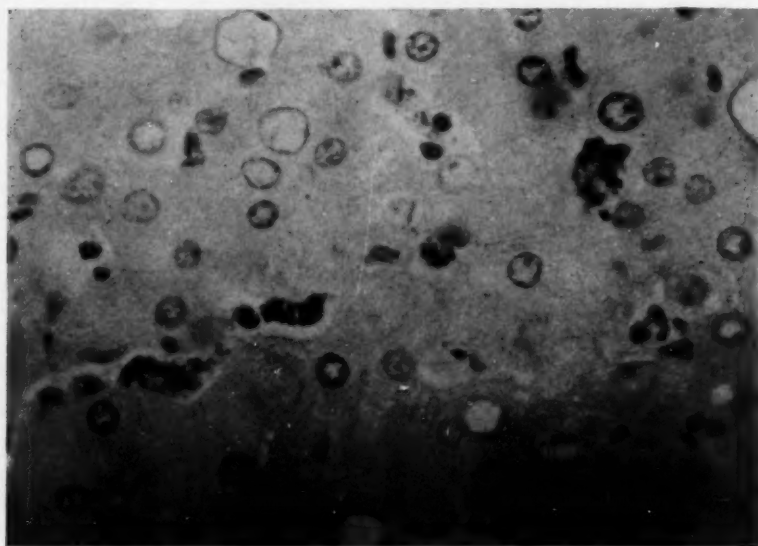


Fig. 4.—Section of the liver from the same patient as in figure 3, after the injection of dextrose. Note the large detached Kupffer cells with the abundant store of india ink.

In view of the tremendous amount of literature on the clinical value of the intravenous injection of dextrose, it seems surprising that so far no attempt has been made to determine scientifically the means by which it is of value to the body. It seems to us that dextrose could be of value in only two ways: (1) as a fuel and (2) as a stimulant of the defense mechanism. Regarding the former, a subsequent paper will demonstrate the inability of the body to utilize as a fuel post-operatively intravenously injected dextrose. Its value as a stimulus is demonstrated by our histologic observations.

2. Mayer, E. G., quoted by Mühlmann, E.: *Strahlentherapie* **27**:307, 1928.

CONCLUSIONS

The intravenous injection of dextrose elicits changes in the Kupffer cells. These changes are indicative of enhanced functional activity. The beneficial clinical effects of the intravenous injection of dextrose postoperatively are attributed to the stimulation of the reticulo-endothelial system.

NEGATIVE EFFECT OF LIVER EXTRACT ON RATE
OF DIVISION OF THE RED BLOOD CELL
IN CHICK BLASTODERMS *

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In a preliminary report by Sabin, quoted by Cohn, Minot, Alles and Salter,¹ suggestive evidence was presented that liver extract effective in pernicious anemia increased the rate of division of the megaloblast in living chick embryo. She reported:

In a series of 266 early blastoderms mounted in Locke solution, to which had been added chicken bouillon as prepared by Lewis and Lewis, no second division of the cells of a given blood island was observed in intervals of from 3 to 6 hours.² . . . In three successive preparations in which extract (Preparation XL R) had been added to the medium a second cell division was seen. In two preparations the second division was of a blood island and the interval approximated three hours; in the third preparation the second division was of an endothelial cell, making the wall of the vessel, and the interval was approximately one hour. The preparations were fixed just as the second cell division was observed and they confirm the observation that the blood islands in the two preparations and the endothelium in the third were in a cycle of cell division. In all of these chicks the heart action remained very vigorous throughout the experiment, so that there was no sign of any toxic substance involved. This material is interesting inasmuch as the blood islands during the stages studied are made up entirely of the megaloblast.¹

This observation, if verified, would be of fundamental importance, because it might furnish a method, urgently needed, for testing the potency of material effective in pernicious anemia, and it might also indicate the possible action on red blood cells of the principle effective in pernicious anemia.

The present study on the normal rate of division in the megaloblast was undertaken at the request of Dr. Sabin, to whom I am indebted for knowledge of the technic and for advice pertinent to such a study. Her preliminary observations as quoted have been verified, but no evi-

* Submitted for publication, Feb. 19, 1930.

* From the Thorndike Memorial Laboratory, Boston City Hospital.

1. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **77**:325, 1928.

2. Sabin, F. R.: Studies on the Origin of Blood Vessels, and of Red Blood Corpuscles as Seen in the Living Blastoderm of Chicks During the Second Day of Incubation, *Contrib. Embryol., Carnegie Institution, Washington, D. C.*, **9**:213, 1920.

dence has been obtained that liver extract promotes the rate of division of the megaloblast in the chick embryo. The misconception was due to the fact that Dr. Sabin did not have opportunity to make adequate control observations on the normal rate of division of the young red blood cell in the living chick embryo.

METHODS AND PROCEDURE

The preparation of the chick embryo and the solutions used were essentially the same, with minor modifications, as those described by Sabin in her excellent monograph on the origin of blood vessels and of red blood corpuscles in the blastoderm.² The preparation of the Locke-Lewis solution was modified to prevent a tendency toward the formation of a precipitate when the solution was sterilized in the autoclave. Satisfactory results were obtained by autoclaving each ingredient separately and, after cooling, mixing them in proper proportions under sterile precautions, then transferring 10 cc. into sterile test tubes. The Locke-Lewis solution thus prepared was kept in the icebox, and bacterial contaminations were not encountered, as shown by frequent tests for bacterial growth. This modification of the preparation of the Locke-Lewis solution obviated daily mixing and sterilization, in spite of which precipitation in the solution could not always be avoided.

OBSERVATIONS

The living chick blastoderm was studied for a variable length of time, usually until the second cell division in a blood island had been observed. The criteria for division of the red blood cells have been admirably described by Sabin for chick embryos. Thus, in the resting stage, the young blood island shows no definite cell outlines but looks like a homogeneous, somewhat glandular mass, often with a definite border. After an interval of time, the mass becomes refractive, the cell outlines become distinct, and mitotic figures can be observed. The actual cell division then occurs. This final process may be rapid and is often not noticed unless attention is directed constantly to certain cells in a given area. After cell division has occurred, the cells lose their refractivity, cell outlines and individuality, and become dull looking and indistinct. Photographs of drawings of the blood islands during various stages of cell division appear in Sabin's monograph.² In no instance was crenation of the red blood cells or laking of the hemoglobin detected.

In the present study, the attention was focused, as a rule, on a few cells, and cell division was looked for, when possible, in the same cells, while in addition the general cycles of cell division were observed. The observations on the division of cells in the living chick embryo were verified in fixed and stained preparations. In many instances the preparation was not fixed until the actual division had taken place, while others were fixed when many mitotic figures were present.

The intervals of time between the cell divisions of the red blood cells in apparently normal chick embryos and explanatory data are

set forth in the table. The table is arranged according to the length of time observed between the first and the second cell division. The first cell division after mounting occurred within one-half hour in twenty-nine of the forty-six preparations studied and recorded. This fact suggests that perhaps the mechanical stimulation of washing and mounting the embryo may have some influence in hastening the process of cell division.

The Rate of Division of the Megaloblast in the Normal Chick Embryo

Preparation*	Time of Incubation		Interval Between Mounting and First Cell Division, Minutes	Interval Between First and Second Cell Division, Minutes	Number of Somites at Time of Fixation	Remarks
	Hours	Minutes				
13 B	48	40	25	45	25	Single cell island
4 B	48	50	10	60	20	Single cell island
15 B	48	60	30	60	21	Small cell island
15 A	48	55	5	60	19	
16 B	48	10	25	65	10	Small cell island
23 B	52	30	25	70	17	Large cell island
17 A	50	18	20	70	21	Small cell island
46 A	47	40	15	75	..	Small cell island
12 B	49	20	50	80	19	Small cell island
22 B	49	30	5	80	..	Medium-sized cell island
3 B	47	25	25	85	10	Small cell island
5 B	60	20	30	85	..	Small cell island
10 B	48	25	40	90	20	Small cell island
24 B	47	30	65	90	10	Small cell island
47 A	47	45	60	90	24	Single cell island
48 A	47	55	40	90	21	Small cell island
2 B	48	15	50	95	20	Medium-sized cell island
8 A	47	00	30	100	20	Medium-sized cell island
75 A	51	15	110	100	21	Large cell island
211 A	47	30	15	100	24	Large cell island
212 A	47	15	30	100	25	Large cell island
1 B	46	45	50	105	18	Large cell island
18 A	48	40	20	105	16	Medium-sized cell island
32 B	48	20	30	110	11	Small cell island
28 B	49	00	20	115	19	Medium-sized cell island
7 A	50	35	35	115	21	Small cell island
53 A	47	55	20	115	21	Medium-sized cell island
241 A	46	30	55	115	..	Medium-sized cell island
26 B	48	00	10	120	17	Small cell island
224 A	43	15	40	120	20	Large cell island
13 A	46	45	25	130	23	Large cell island
225 A	45	55	30	130	22	Small cell island
95 A	46	05	30	135	18	Small cell island
240 A	45	30	60	140	..	Medium-sized cell island
35 B	49	35	20	145	21	Small cell island
22 A	50	00	30	150	21	Medium-sized cell island
73 A	48	15	60	170	17	Large cell island
19 A	49	20	25	180	19	Large cell island
9 B	68	15	100	...	20	Small cell island
21 B	50	10	140	...	18	Large cell island
33 B	51	45	10	...	10	Medium-sized cell island
39 B	48	25	10	...	23	Small cell island, nuclei distinct
12 A	49	10	110	...	16	Medium-sized cell island
56 A	44	45	45	...	18	Large cell island
74 A	48	50	20	...	18	Large cell island

* "A" after the number of the preparation refers to a series done between May and August, while "B" designates a series during the months of March and April.

From an examination of this table in which the figures of time have been expressed in the nearest round number, it may be seen that the interval of time between the first and the second cell division in thirty-nine preparations of living chick embryo varied between forty-five minutes and three hours. The age of the blastoderm when mounted was

usually approximately 48 hours but varied from 43 to 69 hours. In four preparations studied long enough for a second cell division to occur none was observed.

A correlation was made between the size of the group of cells observed and the interval of time between cell divisions. In a general way, the interval between two cell divisions was shorter in the case of single cells, or small islands, although an absolute correlation cannot be made out. A considerable variation occurred also in the size of embryos of the same age, as is indicated by the total number of somites.

The interval of time between the cell divisions of young red blood cells in eight chick embryos mounted in Locke-Lewis solution and the identical liver extract (preparation XLR) used by Dr. Sabin was found to be between 80 and 130 minutes. Dr. Edwin J. Cohn supplied the liver extract.

It is thus evident that although the observations of Sabin on the rate of division of the megaloblast in the chick embryo mounted in Locke-Lewis solution and the identical liver extract in the same dilution were confirmed, this rate of cell division does not seem to differ from that of the normal cell division of megaloblasts of blastoderms mounted in Locke-Lewis solution only. Consequently, this procedure gives no information concerning the potency of liver extracts, nor can any conclusions be drawn from such observations as to the influence on the megaloblast of the active principle effective in pernicious anemia. From the observations described, no evidence has been obtained to suggest that an increased rate of cell division occurs in young red blood cells of the chick subjected to the direct influence of liver extracts potent in pernicious anemia.

CONCLUSIONS

The interval of time between cell divisions in young red blood cells in the normal blastoderm varied from forty-five minutes to three hours. The rate of division was apparently not influenced when liver extract effective in pernicious anemia was added to the mounting fluid.

TERATOMA AND TERATOID TUMORS OF THE BRAIN *

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Intracranial new growths of bidermal or tridermal origin are among the rarest of tumors. There is no mention of a teratoma in the 99 case reports compiled by White¹ from the records of Guy's Hospital for the years from 1872 to 1884. Frankl-Hochwart² in 1909 found only 2 cases of teratoma, or 2.1 per cent, among 97 collected cases of hypophyseal tumors. In Cushing's³ list of 868 verified intracranial tumors, there were 4, or 0.5 per cent. Since 1916, few cases have been reported. The pituitary and the pineal glands seem to be the sites of predilection for these teratoids and teratomas. The case here reported is unique in that the teratoma apparently arose from the cerebellum. Dr. W. M. Baldwin of the department of anatomy of Albany Medical College, to whom the brain was originally submitted, permitted me to study the specimen.

REPORT OF A CASE

History.—W. M., a white man, aged 27, was admitted in 1918 to the service of Dr. Charles Bernstein, Rome State School (Rome, N. Y.), an institution for mental defectives. His mental peculiarity was first noticed when he was an infant. He had never been able to walk. He first talked when 3 years old and in school was able to reach the second grade. He was obedient, industrious but inadequate, considerate, sensitive, affectionate, adaptable and clean.

His father, an inmate of the Brunswick Home, had Huntington's chorea. His mother died at the age of 51 years from "brain abscess," after being ill for three months. Four brothers and four sisters were living and in good health.

Physical Examination.—Physical examination showed a hydrocephalic dwarf, 4 feet (122 cm.) in height, with kyphosis and right lateral curvature of the spine. The jaw was of the prognathous type, and the forehead was high and bulging. The anteroposterior diameter of the head measured 24 cm., the anteroposterior

* Submitted for publication, Feb. 11, 1930.

* From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital.

1. White, W. H.: One Hundred Cases of Cerebral Tumor with Reference to Cause, Operative Treatment, Mode of Death and General Symptoms, Guy's Hosp. Rep. **43**:117, 1886.

2. Frankl-Hochwart, L. von: Die Diagnostik der Hypophysistumoren ohne Akromegalie, Wien. med. Wchnschr. **59**:2326, 1909.

3. Cushing, H.: Notes on a Series of Intracranial Tumors and Conditions Simulating Them; Tumor Suspects; Tumors Unverified; Tumors Verified, Arch. Neurol. & Psychiat. **10**:605 (Dec.) 1923.

curve 45 cm., the binauricular curve 40 cm., the maximum transverse diameter 19.5 cm., and the greatest circumference 70 cm., giving a cranial capacity of 1,364 cc. and a cephalic index of 0.81. The bridge of his nose was low, the palate high and broad. An excess of hair was present over the body. The patient was poorly developed but well nourished; the muscles were flabby; the skin was smooth and moist.

The chest showed poor development; the amount of chest expansion was only 1 inch (2.5 cm.). The point of maximum cardiac intensity was in the fourth interspace; the right border of the heart was 1 cm. to the right of the midsternal line; the left border, 10 cm. to the left of the midsternal line. The heart sounds were muffled, but regular. The blood pressure was 108 systolic and 80 diastolic. The abdomen was not remarkable. The lower extremities were shrunken and useless.



Fig. 1.—Drawing of right mesial aspect of brain. The location of the cerebellar tumor and its general relationship to surrounding structures are clearly shown. Note the enormous communication between the lateral ventricles.

The pupils were equal and regular. Sight was good. The patient was able to hear the ticking of a watch held 2 feet (60.9 cm.) from each ear. He distinguished between the odors of lemon, cinnamon and peppermint. He differentiated between sour, sweet and bitter. His speech was normal. The pain, touch and stereognostic senses were normal. The corneal, pharyngeal, umbilical, plantar, elbow, wrist, supinator and bicipital reflexes were all positive. The knee reflexes were exaggerated. The tongue protruded straight. The strength of his grip was 40 pounds (18.1 Kg.) for the right and left hands.

The Wassermann test of the blood was negative. The hemoglobin was 80 per cent, with a polymorphonuclear differential count of 74 per cent.

The results of the Binet-Simon test were as follows: The patient was extremely nervous, talked plainly and seemed rather bright. He was handicapped

in not being able to read readily, but appeared intelligent otherwise. He was able to cooperate and concentrate well and had clean habits. His mental age was calculated at 8 years and 4 months when his physical age was 27 years; and later at 10 years when his physical age was 29; in other words, he had definite feeble-mindedness of the moron type.

During his five years' stay at the State School, he had parotitis, diphtheria and measles. At various time, he complained of severe headaches with vomiting, and of pains in the stomach and in the back, and he had subnormal temperatures of 96.4 F. In 1923, he developed influenza with a terminal fatal bronchopneumonia.



Fig. 2.—Photomicrograph of a section of the tumor with two large cysts lined by stratified squamous epithelium. It shows hair follicles, sebaceous glands and fatty tissue. The cerebellar leaf at the extreme left indicates the intimate relationship between it and the tumor tissues. Hematoxylin and eosin stains; $\times 31$.

Necropsy.—The necropsy was limited to the head. The brain was examined after fixation in a dilute solution of formaldehyde, U. S. P. (1:10). The dura mater was of the thinness of paper and remarkably transparent like a thin sheet of celluloid wrapped around the brain. The sulci were everywhere shallow, being mere depressions. The convolutions were plateau-like and broad, and averaged 19 mm. in width. The brain with the dura weighed 1,358 Gm. The occipitofrontal diameter measured 20.3 cm., the bitemporal diameter 17 cm. and the sagittal

diameter at about the level of the fissure of Rolando 13.5 cm. The lateral ventricles were enormously dilated, the brain being 4 mm. thick at the vertex, 14 mm. thick at the frontal pole and 30 mm. thick at the occipital pole. By actual measurement, the total capacity of both lateral ventricles was 1,070 cc. The third ventricle was dilated from side to side, so that the massa intermedia was stretched out into a slender cord, 22 mm. long with a diameter of 1 mm. In fact, it appeared as if the third ventricle were but a loculus of the greatly distended lateral ventricles. The foramen of Monro had been converted into an enormous communicating channel. The triangular fourth ventricle measured 2 cm. at the



Fig. 3.—Photomicrograph of a section of the tumor to show true bone formation with lacunae, haversian canals and marrow spaces. Nearby there are two cysts lined by squamous epithelium, and a sebaceous gland. Hematoxylin and eosin stains; $\times 31$.

base and 1 cm. in height. The caudal portions of the fourth ventricle were pressed together by a cystic tumor, originating in the inferior cerebellum and occupying the area of the cisterna magna, which had become obliterated (fig. 1). This tumor completely blocked the exit of the cerebrospinal pathway, producing a massive internal hydrocephalus. The growth measured 3 by 3.5 by 2.8 cm. It was covered by a thin shell of cerebellar tissue, except where it abutted on the roof of the fourth ventricle in apposition to the tela choroidea. On sagittal section, the cyst wall consisted of a thin fibrous layer, less than 1 mm. thick. How-

ever, the thicker portions lay in the white matter of the cerebellum, from which there was no definite delimitation of the tumor tissue. Indeed, here a bony nodule, 4 mm. in its widest dimensions, and numerous hairs seemed to be embedded in the cerebellar substance itself. The contents of the larger cystic mass consisted of strands of light brown hair and degenerating cellular debris. There were several other minute cystic spaces. In addition, islands of fatty tissue could be recognized grossly. The pineal and pituitary glands were not remarkable.

Microscopic Observations.—Before staining, all the sections were first mordanted over night in potassium dichromate solution. Besides the routine stains

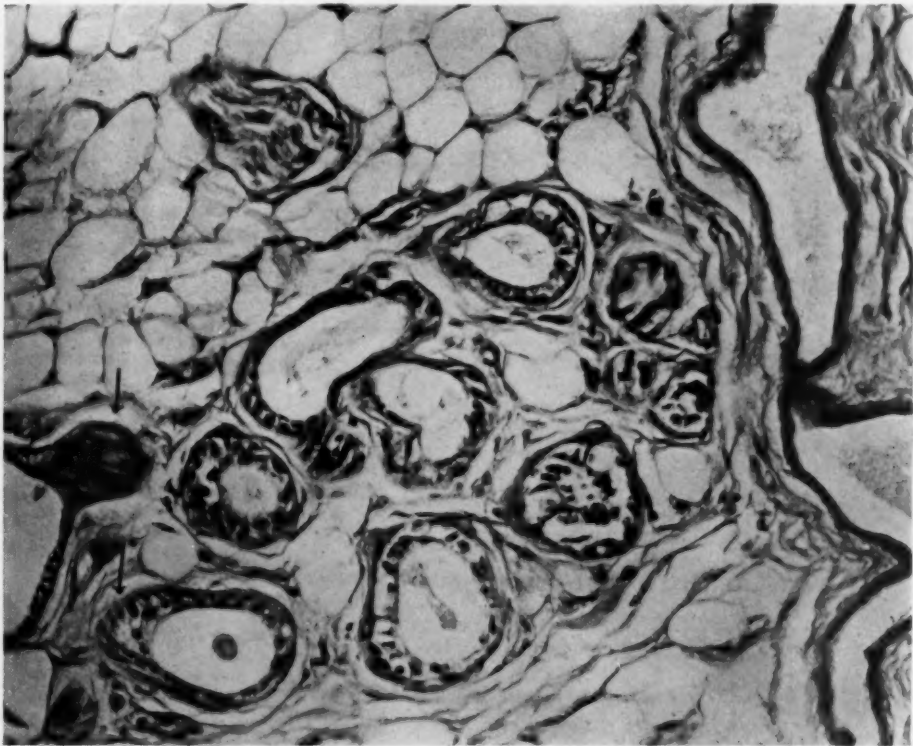


Fig. 4.—Photomicrograph of the fatty portion of the tumor to show the goblet cells lining the tubules, which contain a mucoid secretion. The arrows point to tubules cut obliquely, showing the outer single layer of smooth muscle cells. To the right, there are two large veins. Near the upper left hand corner is an obliquely cut strand of nerve fibers. Hematoxylin and eosin stains; $\times 265$.

with hematoxylin and eosin, I used van Gieson's picric acid-fuchsin, Mallory's phosphotungstic acid-hematoxylin, Weigert's resorcin-fuchsin, Foot and Menard's silver carbonate method⁴ and Penfield's combined method.⁵

4. Foot, N. C., and Menard, M. C.: A Rapid Method for the Impregnation of Reticulum, *Arch. Path.* **4**:211 (Aug.) 1927.

5. Penfield, W.: A Method of Staining Oligodendroglia and Microglia, *Am. J. Path.* **4**:153, 1928.

TABLE 1.—Summary of Observations on Recorded Teratomas

No.	Author	Sex	Age	Location of Tumor	Size of Tumor	Endodermal Structures	Mesodermal Structures	Entodermal Structures
1	Coats: Tr. Path. Soc. London 38 : 44, 1886	M	13 years	Pineal	1½ by 1½ by 1¾ in. (4.7 by 2.50 by 3.1 cm.)	Epithelial pearls (?)	Cartilage, smooth muscle and spindle cell sarcoma	Goblet cells
2	Gauderer: Zur Casuistik der Zirkeldrüesentumoren (Teratoma glandulae pinealis) Inaug.-Dissertation, Gießen, 1889	M	12 years	Pineal	3.5 by 2.5 by 2.5 cm.	Squamous cells and sweat glands (?)	Connective tissue, smooth muscle, cartilage, bone, osteoid tissue and fat	Goblet cells
3	Saxer: Beitr. z. path. Anat. u. z. allg. Path. 20 : 390, 1893	F	7 weeks	Third ventricle	8 by 10 by 12 cm.	Fetal brain tissue, embryonal choroid plexus, squamous epithelium, embryonal eye (?), nerves and ganglion cells	Embryonal connective tissue, striated and smooth muscles, cartilage, bone and fetal blood islands (?)	Goblet cells and embryonal chorda
4	Gutzelt: Ein Teratom der Zirbeldrüse. Inaug.-Dissertation, Königsberg, 1893	M	7½ years	Pineal	4 by 3.25 cm.	Squamous epithelium, sweat glands and hair follicles	Very cellular connective tissue, striated and smooth muscles, fat cells and cartilage	Goblet cells
5	Kon: Beitr. z. path. Anat. u. z. allg. Path. 44 : 233 1908	M	37 years	Pituitary region	Hazelnut	Squamous epithelium, ependymal cells, nerve fibers and glia tissue	Connective tissue, cartilage and bone	Chorda-like tissue
6	Frankl-Hochwart: Deutsche Ztschr. f. Nervenh. 37 : 454, 1909	M	5½ years	Pineal	5 by 2.5 by 2.9 cm.	Epidermis	Embryonal cartilage with ossification and stroma suggestive of spindle cell sarcoma	Goblet cells
7	Fukuo: Ueber die Teratome der Glandula pinealis. Inaug.-Dissertation, München, 1911	M	19 years	Pineal	Walshnut	Squamous epithelium, sweat glands and hairs	Connective tissue, striated and smooth muscles, cartilage, bone with myeloid tissue in marrow and osteoid tissue	Goblet cells
8	Schmincke: München. med. Wchnschr. 61 : 2043, 1914	M	19 years	Pineal	Walshnut	Three germ layers said to be represented		

	9	Schmincke	M	22 years	Pineal	Welshnut	Neuro-epithelium and ganglion cells	Connective tissue	High mucus-forming cylindric cells
	10	Odernatt: Zur Diagnostik der Zirkeldrüsenerkrankungen. Inaug.-Dissertation, Zürich, 1915	M	10 years	Pineal	3 by 2.4 by 2.7 cm.	Squamous epithelium	Cellular connective tissue, smooth muscle and cartilage	Goblet cells
	11	Barron: J. Cancer Research 1: 311, 1916	M	19 years	Pineal	4.2 by 3 by 4.4 cm.	Squamous epithelium, salivary glands (?), hair follicles (?) and ganglion cells (?)	Connective tissue, striated and smooth muscles, cartilage and bone	Goblet cells
	12	Rosco: Proc. Pan-Am. Sc. Cong., Washington, 1917, vol. 10, pp. 522-528	M	30 years	Region of tuber cinereum	4 by 2 by 3 cm.	Hornified epithelium	Connective tissue and fat	Chorda tissue
	13	Boehm: Frankfurt. Ztschr. f. Path. 22: 121, 1919	M	9 1/4 years	Pineal	5 cm. in diameter	Squamous epithelium, embryonal teeth, ependymal rosettes, glia and young ganglion cells	Connective tissue, smooth muscle, cartilage and lymph follicles (?)	Goblet cells and respiratory tract epithelium
	14	Frank: Berl. klin. Wchnschr. 57: 888, 1920	M	20 years	Pineal	34 by 23 by 23 mm.	Hornified squamous epithelium and glia	Connective tissue, smooth muscle and cartilage	Intestinal and respiratory tract epithelium
	15	Luce: Deutsche Ztschr. f. Nervenh. 68-69: 187, 1921	F	5 1/4 years	Pineal	Large plum	All three germ layers said to be represented		
	16	Klaproth: Centrabl. f. allg. Path. u. path. Anat. 32: 617, 1922	M	15 1/4 years	Pineal	Small apple	Squamous epithelium, embryonic medullary tube, sebaceous glands and hairs	Connective tissue, smooth muscle and bone with myeloid tissue in marrow	Goblet cells
	17	Derman: Virchows Arch. f. path. Anat. 259: 767, 1925	?	1 month	Choroid plexus	Child's fist	Epidermis, pigmented epithelium, embryonal choroid plexus (?) and glia (?)	Connective tissue, striated bone and fat	Goblet cells
	18	Hosol	M	27 years	Cerebellum	3 by 3.5 by 2.8 cm.	Squamous epithelium, sebaceous glands, sweat glands (?), hair follicles and nerve fibers	Connective tissue, smooth muscle, bone with marrow and fat	Goblet cells

TABLE 2.—Summary of Observations on Recorded Teratoid Tumors

No.	Author	Sex	Age	Location of Tumor	Size of Tumor	Ectodermal Structures	Mesodermal Structures	Structures Hard to Evaluate
1	Maier: Virchows Arch. f. path. Anat. 20 : 536, 1891	M	10 weeks	Left cerebral hemisphere	Apple	Epithelium, sebaceous glands and hair	Connective tissue with malignant changes, cartilage and bone	
2	Weigert: Virchows Arch. f. path. Anat. 45 : 212, 1875	M	14 years	Pineal	3.5 by 3.5 by 3 cm.	Epidermis, sebaceous glands, hair follicles and nerve fibers	Connective tissue, smooth muscle, cartilage and fat	Cysts lined with cylindrical epithelium
3	Falken: Virchows Arch. f. path. Anat. 75 : 350, 1879	M	16 years	Pineal or choroid plexus (?)	5.8 by 4.7 by 3 cm.	Ependyma and tela choroida (?)	Spindle cell sarcoma and cartilage	
4	Beck: Ztschr. f. Heilk. 4 : 393, 1883	F	74 years	Pituitary	2.5 by 2.7 by 2.4 cm.	Fourteen teeth	Myxomatous tissue, cartilage and bone	Cysts lined with ciliated epithelium
5	Sainsbury: Tr. Path. Soc. London 37 : 57, 1886	Base of brain	Walnut	Epidermis	Connective tissue and fat cells	Numerous round cells
6	Strassmann and Strecker: Virchows Arch. f. Path. Anat. 108 : 351, 1887	M	3 years	Choroid plexus	Walnut	Epithelium, adnons and tubular glands, ganglion cells, glia cells and nerves	Connective tissue, striated and smooth muscles, cartilage, bone, fat and lymphatic tissue	Cysts lined with one layered to several layered epithelium, ciliated epithelium
7	Eberth: Virchows Arch. f. path. Anat. 153 : 71, 1898	F	75 years	Inner surface of dura	Split pea	Nerves	Muscle, fat and lymphoid tissue	
8	Benda: Berl. med. Wchnschr. 37 : 1265, 1900	M	38 years	Pituitary	Walnut	Squamous epithelium	Connective tissue and bone	
9	Neumann: Ein neuer Fall von Teratom der Zirbel druese, Inaug.-Dissertation, Koenigsberg, 1900	M	27 years	Pineal	4 by 3.5 cm.	Squamous epithelium	Connective tissue, striated and smooth muscles, cartilage, fat and lymphoid tissue	Glands lined by cuboidal to high columnar epithelium
10	Rows: Rev. Neurol. & Psychiat. 4 : 339, 1906	M	77 years	Frontal lobe	1 inch (2.5 cm.) in diameter	Epithelium	Fibrous tissue and fat	
11	Rows	M	73 years	Frontal lobe	Hen's egg	Skin, sebaceous glands and hairs	Elastic tissue, muscle, fat, embryonal blood vessels, cartilage and bone	

		F	48 years	Pituitary	2 cm. in diam- eter	Epithelioma and glia	Connective tissue and bone
12	Bregman and Steinhaus: Vir- chow's Arch. f. path. Anat. 188: 330, 1907						
13	Hecht: J. A. M. A. 53: 1001 (Sept. 25) 1909	F	11 years	Pituitary	% by 1 inch (1.9 by 2.5 cm.)	Epithelium and sal- vary glands (?)	Embryonal connective tis- sue and giant cells
14	Bailey and Jelliffe: Arch. Int. Med. 8: 851 (Dec.) 1911	M	12 years	Pineal	1.5 inches (3.75 cm.) in diameter	Sebaceous material and hairs	Cartilage
15	Cushing: The Pituitary Body and its Disorders, Philadelphia, J. B. Lippincott Company, 1912	F	16 years	Pituitary	Golf ball	Myxomatous tissue, car- tilage and bone
16	Cushing	M	35 years	Pituitary	5 cm. in diameter	Myxomatous tissue, embryonic cartilage and few bone cells
17	Van den Bergh and Van Has- selt: Nederl. tijdschr. v. geneesk. 1: 1271, 1913	M	8 years	Pineal	Small marble	Squamous epithelium, sebaceous glands, hairs and nerve tissue	Connective tissue, carti- lage and bone
18	Burmeister: Bull. Johns Hop- kins Hosp. 26: 410, 1915	M	60 years	Choroid plexus	4.7 by 2.5 by 3.5 cm.	Multilayered epithelium and epithelioma	Hyaline cartilage and brain sands
19	Kato: Jahrb. f. Psychiat. 35: 45, 1914	F	16 years	Cerebello- pontile angle	Pigeon egg	Hornified epithelium and ganglion cells	Connective tissue, muscle, fat and bone
20	Sztanolevits: Neurol. Centralbl. 37: 784, 1918	M	32 years	Cerebel- lum	Man's fist	Gland tissue (?) and hairs	Bone and fat
21	Globus: Arch. Neurol. & Psychiat. 9: 417 (April) 1923	F	6 years	Pituitary	4 by 3.5 cm.	Squamous epithelium, salivary glands (?) and sebaceous glands (?)	Mucoid connective tissue, embryonal cartilage and bone with marrow
22	Horrax and Bailey: Arch. Neurol. & Psychiat. 13: 423 (April) 1925	M	3 years	Pineal	Horny epithelium, sebaceous glands and hairs	Cartilage, bone and fat
23	Kraus: Virchows Arch. f. path. Anat. 271: 546, 1929	F	Premature	Pituitary region	37 by 30 mm.	Neuro-epithelial tubules, glia, choroid plexus and embryonal eye (?)	Embryonal connective tis- sue, striated muscle (?), cartilage and bone
							Cysts lined by one layered to several layered cylindric epithelium

The large cyst and the smaller cystic spaces were all lined by stratified squamous epithelium. Beneath this epithelium, there were islands of well developed sebaceous glands and hair follicles (fig. 2). A few rudimentary tubular sweat glands were present in one location near an epithelial cyst. These cysts contained necrotic cellular debris. Cholesterol crystals were present here and there in the more fibrous connective tissue matrix, which consisted mostly of collagen with a few elastic fibrils, as shown by van Gieson's and Weigert's stains. Elastic fibrils, however, were found most abundantly in the loose connective tissue layer just beneath the squamous lining of the various cysts. Several of the sections showed true bone formation with typical lacunae and haversian canals (fig. 3). A few strands of smooth muscle cells could be identified, which stained yellow by van Gieson's method. There were many small spaces lined by cells, varying from cuboidal to columnar, which were difficult to identify. In one group of tubules lying in an island of fat, the lining cells were of the typical goblet cell type (fig. 4). Each tubule was surrounded by a single layer of smooth muscle cells (stained yellow by van Gieson's method), which ran parallel with the lumen of the tubule, best seen when the sections were cut obliquely or at a tangent to these tubules. This association of goblet cells and smooth muscle strongly indicated a derivation from the intestinal anlage. Large areas of fatty tissue were present. Blood vessels and small bundles of myelinated nerves were seen throughout the various sections. Fine strands of reticulum were demonstrable by the Foot and Menard silver stain in the loose connective tissue stroma, in the fatty tissue and in the walls of blood vessels.

In those areas near the periphery of the tumor in which there was an admixture of teratomatous structures and cerebellar tissue, the increase in neuroglia fibrillae was prominent, as shown by Mallory's phosphotungstic acid-hematoxylin. There was also a marked reactive gliosis in the sections from the brain stem, but only a moderate one in the cerebral cortex. In the sections of the cerebellum and cortex stained by the Penfield method, microglia and oligodendroglia were not significantly altered. The cortical ganglion cells and capillaries appeared much increased in number. This increase may have been only apparent, since the cortex had been markedly thinned by pressure from the internal hydrocephalus. The ganglion cells were well supplied with chromidial substances which showed no microscopic evidence of chromatolysis.

COMMENT

From table 1, it is seen that tridermal tumors or genuine teratomas of the brain are extremely rare. I have been able to find reports of 17 instances in the literature, in 2 of which no detailed microscopic observations were given. On the other hand, teratoid tumors, though rare, occur more often, 23 such cases being recorded. Owing to the varying degrees of complexity and to the frequently undifferentiated character of these types of tumors, it is difficult to evaluate and classify many of the structures found in teratomatous and teratoid growths. From a study of the literature, it is seen that many do not differentiate between genuine teratomas and teratoid tumors. Yet one must take into consideration that a tumor which at one examination is obviously monodermal, owing to a marked overgrowth and proliferation of the derivatives of one germ layer at the expense of the other two primitive

layers, may have been tridermal in the beginning. Askanazy⁶ considered his case of primary pineal chorio-epithelioma to be teratomatous, which makes this tumor an ectodermal derivative. Goldzieher,⁷ on the other hand, interpreted his similar case as an angioblastic sarcoma, hence mesodermal in origin. Ewing⁸ stated that a partially choriomatous structure is produced in testicular tumors by alterations in the cylindric cell lining of blood spaces, that smooth and striated muscles are occasional elements of the normal epiphysis, that ependymal epithelium may become high and cylindric or flat and squamous and that all the elements of these complex tumors, except dermal structures, may be derived from the pineal gland itself. However, he believed that misplaced tissue may rest in the pineal and pituitary glands. White's⁹ case of ganglioneuroma and Pappenheimer's¹⁰ case of neuroglioma ependymale of the pineal gland showed the presence of muscle fibers, but as has been pointed out by Ewing and by Pappenheimer himself, one is not justified in calling these tumors bidermal because of this. The data furnished by Bowlby,¹¹ Ogle¹² and de Monchy¹³ are meager and somewhat uncertain. Takeya's¹⁴ and Kishenski and Tisenhausen's¹⁵ articles are inaccessible. Schmincke and Luce merely mentioned that derivatives of all three germ layers were found in their cases, and Hueter¹⁶ that microscopically the pineal tumor was a tera-

6. Askanazy, M.: Teratom und Chorioepitheliom der Zirbel, *Verhandl. Deutsche path. Gesellsch.* **10**:58, 1906.

7. Goldzieher, M.: Ueber eine Zirbeldruesengeschwulst, *Virchows Arch. f. path. Anat.* **213-214**:353, 1913.

8. Ewing, J.: *Neoplastic Diseases*, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 949.

9. White, W. H.: A Myo-Neuroma of the Pituitary Body, *Tr. Path. Soc. London* **36**:37, 1885.

10. Pappenheimer, A. M.: Ueber Geschwülste des Corpus pineale, *Virchows Arch. f. path. Anat.* **200**:122, 1910.

11. Bowlby, A. A.: Tumor of the Pituitary Body, *Tr. Path. Soc. London* **36**:35, 1885.

12. Ogle, C.: (1) Sarcoma of the Pineal Body with Diffuse Melanotic Sarcoma of the Surface of the Cerebrum; (2) Tumor of the Pineal Body in a Boy, *Tr. Path. Soc. London* **50**:4, 1899.

13. De Monchy, S. J. R.: Rhythmic Convergence Spasm of the Eyes in a Case of Tumor of the Pineal Gland, *Brain* **46**:179, 1923.

14. Takeya: *Die Erkrankungen der Epiphysis*, Nisshin-Igaku (Japan), 1913, vol. 3, part 2; cited by Fukuo, Y.: Ueber die Teratome der Glandula pinealis, *Inaug.-Dissertation*, Munich, 1914.

15. Kishenski, D. P., and Tisenhausen, M. M. von: Teratoma of the Cerebellum and Neuroma of the Falx Cerebri in One and the Same Patient, *Med. Obozr.* **74**:807, 1910.

16. Hueter: Teratom der Zirbeldruese, *München. med. Wchnschr.* **60**:895, 1913.

toma. Furthermore, Oestreich and Slawyk's case¹⁷ of psammosarcoma cysticum of the pineal gland was diagnosed as a teratoma by Askanazy. These cases are mentioned here merely for the sake of completeness.

Judged from the recorded cases of teratomas and teratoid tumors, the pineal and pituitary glands seem to produce more tumors than the other intracranial structures. Krabbe,¹⁸ who made an extensive study of the pineal gland, explained this high incidence of epiphyseal teratomas by the fact that during intra-uterine life the germ of the gland comes near the surface, nearer than any other part of the brain, and for this reason there are to a superlative degree conditions facilitating the penetration of foreign tissue elements into the organ. Other less frequently observed locations are the choroid plexus, the tela choroidea of the third ventricle, the brain substance itself, the region of the tuber cinereum, the cerebellum, the cerebellopontile angle and the inner surface of the dura mater. Teratoids and teratomas of the spinal cord are of even rarer occurrence, there being only about six verified cases on record. In the collection of the Albany Medical College, there is a teratoid tumor of the lumbar spinal cord, successfully removed by Dr. Arthur H. Stein, which was associated with a spina bifida occulta and a pilonidal cyst. The microscopic picture showed an overgrowth of smooth muscle cells in which were embedded glandular structures lined by ciliated and non-ciliated cuboidal to columnar cells, some in papillary formation, a few fat cells, nerve fibers and numerous pacinian tactile corpuscles. Intracranial teratomas have also been found in the rabbit by Margulies¹⁹ and Shima.²⁰ Comprehensive teratologic studies have been made by Wilms,²¹ Bostroem,²² Ewing and Heijl.²³ In the case here reported, the cerebellar teratoma was associated with congenital deformities else-

17. Oestreich, R., and Slawyk: Riesenwuchs und Zirkeldruesen-Geschwulst, *Virchows Arch. f. path. Anat.* **157**:475, 1899.

18. Krabbe, K. H.: The Pineal Gland Especially in Relation to the Problem of Its Supposed Significance in Sexual Development, *Endocrinology* **7**:379, 1923.

19. Margulies, A.: Ueber ein Teratom der Hypophyse bei einem Kaninchen, *Neurol. Centralbl.* **20**:1026, 1901.

20. Shima, R.: Ein Teratom in Kaninchenhirn, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **14**:373, 1908; Marburg demonstriert fuer Shima aus Tokio, *Neurol. Centralbl.* **27**:889, 1908.

21. Wilms, M.: Ueber die Dermoidcysten und Teratome, mit besonderer Beruecksichtigung der Dermoide der Ovarien, *Deutsches Arch. f. klin. Med.* **55**:289, 1895.

22. Bostroem, E.: Ueber die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide, *Centralbl. f. allg. Path. u. path. Anat.* **8**:1, 1897.

23. Heijl, C. F.: Die Morphologie der Teratome (Mit besonderer Beruecksichtigung der Zentralnervensubstanz), *Virchows Arch. f. path. Anat.* **229**:561, 1920-1921; Beitrag zur Kenntnis von den Teratomen, *Ergebn. d. allg. Path.* **20**:213, 1923-1924.

where in the body—dwarfism, kyphosis and scoliosis. This association of two or more congenital anomalies is, of course, not an uncommon observation.

In a survey of the literature on the various congenital defects, excluding those of the generative organs, one is struck by the fact that males are generally more frequently affected than females. No acceptable explanation has been offered for this. As shown in table 1 of the teratoma group, there were 15 males to 24 females, with the sex not mentioned in one case. Seventy-eight per cent of the patients were below the age of 20 years. As regards the teratoid tumors (table 2), there were 14 males to 8 females. Over 52 per cent of these were below 20 years in age. The 19 pineal gland tumors, with one exception, have all occurred in the male sex between the ages of 5 1/2 and 27 years. For the pituitary tumors, there were 3 males to 6 females. In regard to sizes, these growths varied from that of a split pea to 8 by 10 by 12 cm. They were generally cystic.

Histologically, ectodermal and mesodermal elements occurred most frequently. The only structures that might be regarded as entodermal were the embryonal tissue resembling the chorda, the cystically dilated spaces lined by tall goblet cells, and the respiratory epithelium in close relation to cartilage. Other entodermal organoid structures have not yet been described as occurring in these intracranial tumors. Among the teratoid tumors, 21 showed both ectodermal and mesodermal structures, while in 2 cases, only the mesoderm was represented. Malignant changes of a sarcomatous nature were described in 4 cases and in 2 an epithelioma.

From tables 1 and 2, it is seen that all of these tumors arose at or somewhere near the midline. It is well known that the midline in the development of the individual has great potentialities for the misplacement of embryonal tissue and its subsequent maldevelopment. Whether the misplaced cells be totipotent or not will naturally depend on how early such misplacements take place. For the cells to be totipotent, this must occur before gastrulation, when the differentiation into ectoderm and entoderm begins.

SUMMARY

Genuine teratomas of the brain are rare. Another case is here reported, showing derivatives of the three primitive germ layers. Clinically, the patient showed dwarfism, kyphosis, scoliosis, hirsutism, marked hydrocephalus and moronic feeble-mindedness. He was never able to walk. The tumor probably originated from some misplaced tissue in the cerebellum. The literature on teratomas and teratoid tumors is reviewed.

General Review

THE LAW OF THE DEAD HUMAN BODY *

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For the pathologist, using this term broadly to include the hospital or university pathologist, the coroner's physician, the autopsy surgeon, as the California coroner's law styles the coroner's physician, the medical examiner, the medicolegal expert and the physician who is called on occasionally to make a postmortem examination, the dead human body is the chief field of labor. That the body is dead when it is brought to the attention of the pathologist is usually evident enough. The body is dead when all evidences of vitality have ceased. For the determination of death the textbooks give a number of classic tests. The application of these, when there is any doubt about the matter of death, usually devolves on the physician who has been in attendance on the deceased at the time of death. The rare instances of suspended animation may occasionally make it necessary for the pathologist to assure himself that the body before him is actually dead. From what appears in the legal literature, and especially in that relating to still-birth, in connection with which the question of death has received most discussion in the law, cessation of respiration is the most important factor in determining the moment or actuality of death. The attitude of the legal mind toward the "breath of life" is somewhat akin to that of the poet or of the philosopher, whose discourse is of the soul.

Although it cannot speak for itself, the dead human body has certain rights and privileges, guaranteed to it by the common law and by statute. It is hedged about with legal restrictions just as is the living body. Some of the rights and restrictions relating to the dead body appertain to it because of the wish of the deceased expressed during life. Others are the results of rights which the kin of the deceased have in his dead body. The purpose of still others is the safeguarding of the public welfare, in order that public decency may not be outraged or the public health endangered. The rights of the dead human body and the rights of others in it, as well as the restrictions relating to it, must be observed by the pathologist as well as by all others.

In its study of matters of medicolegal interest, the Committee on Medicolegal Problems of the Medical Section of the National Research

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Council made a survey of the offices of coroner and medical examiner as those offices function in the United States. The results of this study were presented in a report¹ published in 1928. A second task undertaken by the Committee was to have prepared a digest of laws and court decisions relating to the dead human body. This compilation was made by Mr. George H. Weinmann.² It is on the matter presented by Mr. Weinmann that this review is based, its aim being to present to the pathologist such aspects of the subject as are of interest and importance to him in his work. References to legal writings will, in general, be omitted; when given, they will be in the form adopted in legal writings. The subdivision of the subject matter used by Mr. Weinmann will be adhered to, to facilitate reference to the original bulletin and to the numerous legal citations therein given.

WHAT IS A DEAD HUMAN BODY AND WHEN DOES
IT CEASE TO BE SUCH?

Law, which deals in exact definitions and in finely drawn distinctions which often require court decisions for their interpretation and further precision, does not set down in so many words just what a dead human body is. The term "dead body" is frequently used in the statutes, especially those relating to the coroner, and in general is synonymous with "corpse," derived from the Latin *corpus*, which in its turn means again simply body, but in older religious and philosophic writings, the body as opposed to the soul and such other supermechanistic attributes as the living human being was supposed to possess. The terms "dead body" and "corpse" suggest a human being who has been deprived of life. The signs of death and the tests for determining the cessation of life are described in the textbooks of forensic medicine. Law lays greater stress on the cessation of respiration as an evidence of death than on the extinction of any of the other vital functions.

But the human body from which life has passed does not always remain a dead human body in the legal sense. Court decisions have held that it ceases to be such when it is completely decomposed or disintegrated, and that the laws relating to the disposal of the dead human body no longer apply to the more or less completely disintegrated remains of the human body. After presenting two court decisions pertaining to this subject, Weinmann³ said:

1. Schultz, O. T., and Morgan, E. M.: The Coroner and the Medical Examiner, National Research Council, Bull. 64, 1928.

2. Weinmann, G. H.: A Survey of the Law Concerning Dead Human Bodies, National Research Council, Bull. 73, 1929.

3. Weinmann (footnote 2, p. 10).

Thus, we see that the courts have definitely committed themselves to the rule that mere remains of a body of a person long dead are not to be considered as a dead human body. In the first case the remains were those of an unknown person who had apparently never been buried. In the second case they were those of a person who had once been interred. It is true that in both these cases interpretation of statutes was involved, but these statutes in no way necessitated an unusual interpretation being placed on the terms "dead body" and "corpse."

This is, perhaps, the answer to the facetious question, "When does the removal of human remains from their burial place cease to be grave robbery and become archeology?"

PARTS OF THE BODY

The interpretation of laws relating to parts that have been removed from the living body is a matter of especial interest to the hospital pathologist. In my work as pathologist to hospitals, I have performed my labors under the impression or assumption that parts or organs removed from the body during surgical operations belong to the hospital, on which devolves the duty of making disposal of such parts and which therefore has the right to make such disposal as it may deem best. I had believed that the surgeon, through courtesy, stood next in the line of possession. Such is not the case. Removed portions of the body belong to the person from whom they have been removed. He has the right to specify what disposal is to be made of them, and may bring action to recover damages if the disposal has been contrary to his wishes. The mendacious patient might make this knowledge a source of trouble. It might be well for hospitals and surgeons to protect themselves against the possibility of lawsuit by including in the operating permit, which the patient or his legal representative signs, a statement covering the disposal of parts removed at operation.

The right of the individual to the possession or disposal of parts removed from his body is a right accruing to him under the common law. Positive statutory enactments defining this right of the individual are in force in New York, North Dakota, South Dakota and Oklahoma. The North Dakota statute⁴ relating to this matter, which has been adopted also by South Dakota and Oklahoma and which is almost as restrictive as are the laws governing the disposal of the dead human body, is as follows:

All provisions of this chapter requiring the burial of a dead body or punishing interference with or injuries to a dead body apply to any dead limb or member of a human body, separated therefrom during lifetime.

Since the provisions referred to relating to the dead body require burial permits and permits for removal or exhumation, a strict inter-

4. Section 9623, Compiled Laws of North Dakota, 1913.

pretation of the law quoted would make similar regulations apply to parts removed from the living body.

STILLBIRTHS

Although there is considerable variation in the different states in the definition of stillbirth, the statutory provisions or the regulations of the department of health or vital statistics requiring the registration of such births, in effect in most of the states, make of the body of the stillborn infant a dead human body in the legal sense. The laws relating to the disposal of the dead human body therefore apply to the stillborn infant. Such discrepancy as exists in the laws of the various states centers about the period of uterine gestation that the fetus must have reached before it can be considered a stillbirth rather than a miscarriage. This period varies from the fourth to the seventh month of pregnancy in the different states. In order to bring about uniformity, Weinmann recommended the adoption by all the states of the definition of stillbirth proposed by the International Health Board of the League of Nations. The proposed definition of "birth," "live-birth" and "dead-birth" follows:

It is requisite, in drafting the desired definition, to have a clear understanding of what constitutes a "birth" and when such "birth" is "complete."

In the proposed definition, the word "birth" means the separation and extrusion of a fetus from the body of the parturient woman. The birth is to be deemed complete at the instant when the whole of the body of the fetus—head, trunk, and limbs—is outside the body of the mother.

The birth is to be deemed a live-birth if, after birth (as defined above) the infant breathes.

The act of respiration is incontrovertible evidence of life, and its continued absence is to be taken as proof of foetal death.

It is desirable, for statistical purposes, that a distinction should be made between the birth of a fetus which can normally be expected to be capable of an existence independent of its mother and the expulsion of one which cannot, births in the latter category being regarded as miscarriages (abortions).

A fetus capable of an independent existence is a "viable fetus" and is the product of a gestation which has lasted at least twenty-eight weeks. Such fetus will normally measure at least 35 cm. from the crown of the head to the sole of the heel, the body being fully extended. We are of the opinion that the latter criterion is the more trustworthy.

Hence, a "dead-birth" is the birth of a fetus, after twenty-eight weeks' pregnancy in which pulmonary respiration does not occur; such a fetus may die either: (a) before, (b) during, (c) after birth, but before it has breathed.

Under existing conditions, two criteria obtain in determining in any given case whether the child was stillborn or died immediately after birth. The child must have been completely delivered, that is the cord must have been severed, and independent respiration must have been established if the child is to be considered a living infant. In the

legal sense, an infant who begins to breathe after its expulsion from the vagina, but ceases to breathe before the cord is severed, is stillborn.

Registration of stillbirth makes the stillborn infant a dead human body. The laws regulating the disposal of the latter therefore apply to stillbirths. In many localities, however, they are loosely construed. Disposal to a hospital or to a physician, instead of in a recognized burial place or licensed crematory, is usually permitted. The final disposition made by the hospital or physician may be such as would not be permitted in the case of other dead bodies. Many pathologists probably have the same feeling of lack of legal responsibility in regard to stillbirths as to removed parts of the body. They should protect themselves against mendacity and possible lawsuits by assuring themselves that disposal has been granted in proper legal form before anything is done which might be construed as mutilation of the body.

PROPERTY RIGHTS

The Right of Custody.—The dead human body is not property in the legal sense. It may not be bargained for, bartered or sold. Most states have drastic laws against the sale or illegal possession of the dead human body. It may be disposed of only in such manner as is recognized by law, that is, by interment or cremation, if there is any one on whom the duty of disposal devolves. The right of custody and the duty of legal disposal are concomitant. The right of custody usually follows the laws of inheritance of property, nearness of kinship of surviving relatives determining the custody. The right of custody does not, however, follow the rules of inheritance in all cases. If the deceased had been married but had been separated before death from the surviving spouse, the right of custody rests with the nearest of kin and not with the surviving spouse. Some odd and little known common law provisions relate to the duty of burial, if the deceased had no known relatives or friends on whom the duty of burial devolves. If there are no statutory provisions specifically regulating the disposal of such dead bodies, the common law places the responsibility for burial on the tenant of the building in which the death occurred or on the owner if there was no tenant. Under similar circumstances, the master of a vessel on which death occurred must make proper legal disposal of the body; if there is no master, the owner is responsible. The duty of burial of a person without kith or kin falls on the administrator or superintendent of a hospital in which the death occurs. In most states these common law rules have been superseded by the laws creating state anatomic boards, by laws empowering the coroner to bury if an inquest has been held or by laws providing for the burial of the indigent.

The right of custody and the duty of burial have bearings which are important to the pathologist. They influence the right to give consent for the making of postmortem examination. This matter is discussed in greater detail in a later section.

Testamentary Disposal of the Body.—Although the English law, on which our common law is based, does not recognize the right of a person to dispose of his body by will, most of our states do recognize such a right. New York, North Dakota, South Dakota and Oklahoma have enacted laws specifically granting the right of a person to dispose of his body or parts thereof by will. In other states such right has generally been upheld by the courts. Although the person legally entitled to the custody of the dead body, in the absence of testamentary provision for its disposal, has no property right in the body, the living person does appear to have such a right in his own body. He may specify by will the place of burial of his body or the manner of disposal, whether by burial or cremation. He may require that a necropsy be done. He may dispose of parts of his body for scientific purposes. He may even barter or sell his dead body, receiving payment therefor during life, provided the disposal to be made of his body does not outrage public decency or menace the public health. An interesting court decision⁵ upholds the validity of an insurance policy clause by which the insured grants to the company the right to have a necropsy made if the company deems such an examination advisable.

From the legal point of view questions arising out of violations of the right of custody of the dead body or of quasi property rights in such body are vexatious. They involve the always troublesome problem of money damages for mental pain and suffering when there has been no physical damage. A few jurisdictions recognize no such form of damage. In jurisdictions that do recognize such damage, the amount of money damage allowed may be merely nominal or it may be punitive. The class of case in which this question of violation of rights in the dead body most frequently arises is that in which damages are asked for the making of an unauthorized necropsy. In his discussion of the subject, under the heading, "Remedies," Weinmann⁶ said:

Summing up this whole question of damages, we might say that it seems to be well settled that damages for mental pain and suffering are recoverable for the invasion or violation of, or interference with, the various rights connected with the custody and interment of the dead, despite the fact that it is a well-recognized general rule of damages that mental suffering, in order to be an element of damage, must be connected with some physical injury, and that it must be the proximate result of such physical injury.

However, some violations of rights are not such as could be compensated for. If, for example, the legal custodian of a body were deprived of its possession

5. Weinmann (footnote 2, p. 28).

6. Weinmann (footnote 2, p. 33).

prior to the burial, we have seen that he could bring an action at law for money damages. But ordinarily, that would not satisfy the person aggrieved. Therefore, if he wishes to have the actual possession of the body and not to be compensated for the violation of his rights, he should properly go into a court of equity. There is no general rule to be applied to determine how and when the courts will act in such cases beyond the general principles we discussed when treating the subject of custody. Each case will be decided by an equity court on its own merits, and the general equity principles of substantive and procedural law will be applied. In a court of equity, and only there, can one have his rights specifically enforced.

The Coroner and the Dead Body.—The coroner may be conceded to have absolute control of any dead body which he must view or over which he must hold an inquest. His control is generally conceived to be so broad as to lead to the belief that the body of a human being, whose death he must investigate may not be disturbed or moved until viewed by him or until he has given permission for its removal. So far as disturbance of the body may interfere with the investigation or detection of crime, the matter is important. But neither in common law nor in the statutes of the states and territories of the United States is there any specific statement prohibiting removal of the body. Removal of a dead body over which the coroner has authority might be punishable on the ground that such disturbance is an interference with the proper discharge of the duties of an official or is an attempt to destroy necessary evidence, but the intent to interfere or to destroy evidence would have to be proved. After full discussion of the subject of removal of the dead body over which the coroner has jurisdiction and after presentation of the statute of each state and territory relating to this subject, Weinmann⁷ concluded:

After having gone through this brief résumé of the laws of the various jurisdictions, we note that in very few instances do we find any intimation or express statutory provision, prohibiting the person who may discover a dead human body from moving it prior to a view by the coroner. However, as pointed out at the beginning of this chapter, it has always been a violation of the law to hinder the coroner in the performance of his duties. Therefore, one should never move a body, even where it is permissible, prior to having been granted permission from the proper authorities, unless it becomes absolutely necessary. Mere meddling would not be tolerated in the most liberal-minded jurisdiction. In cases where there is reason to suspect crime, evidence of a very important nature may be destroyed by the slightest disturbance of the body. It is even possible, too, for the person who has a tendency to meddle in this respect to incriminate himself unwittingly.

Therefore, although as a general rule it would appear that there is no prohibition against moving a body, it is compatible with common prudence and wisdom to allow the body to remain in the same position in which it was discovered until the proper authorities have viewed it.

7. Weinmann (footnote 2, p. 57).

Although the section, which is entitled "Coroners and Coroners' Inquests" and of which the quotation given is the conclusion, deals with what may appear to be a question of minor importance, in that it relates chiefly to the removal of the dead body, it contains matter of great value to everyone interested in criminal justice. It gives, for the first time so far as I am aware, a compilation of the statutes of the various jurisdictions of the United States relating to the duties of the coroner.

NECROPSIES

Consent.—The laws which hedge about the dead human body and which protect the rights of those entitled to its custody require consent for the postmortem examination of such a body. The unauthorized performance of a necropsy is a ground for a civil suit for damages and in some states is a violation of the criminal code. The pathologist, who takes pride in his work, who feels that he performs that work with due respect to the dead and to the feelings of the living, and who looks on his work as useful, will probably be amused, perhaps a little painfully, by the following words of a learned judge in rendering a decision in a suit⁸ in which the unauthorized performance of a necropsy was alleged.

The right is to the possession of the corpse in the same condition it was in when death supervened. It is the right to what remains when the breath leaves the body, and not merely to such a hacked, hewed and mutilated corpse as some stranger, and offender against the criminal law, may choose to turn over to an afflicted relative.

It is possible that his amusement may be tinged with indignation at the implied description of his work as a process of hacking, hewing and mutilating the dead body.

In general, the consent for a necropsy may be given by the person who is entitled by law to the custody of the body and who is charged with its burial. This subject has already been discussed, and it was noted that under certain circumstances the tenant or owner of the building, the master or owner of the vessel, or the superintendent of the hospital, in which death took place, is charged with burial. Such a person, therefore, has the right to give permission for postmortem examination. In most states, however, this right is curtailed by the provisions of the anatomical acts which have been made part of the laws of such states.

Consent need not be in writing or in any specified form, unless specifically so provided by legislative or departmental enactment. The consent, even the necessity, to perform a necropsy may be a provision

8. *Foley v. Phelps*, 1 App. Div. (N. Y.) 551.

of the will of the deceased. It has already been noted that a clause in an insurance contract granting to the company the right to demand a postmortem examination has been held valid by the courts. Even without definite statutory provision to that effect, the coroner or medical examiner has the right to authorize a necropsy in any case in which it is necessary for him to determine the cause of death, unless such right has been specifically limited or curtailed by legislative enactment.

Legislative Enactments Relating to Necropsies.—Although the right of the person entitled to custody or of the coroner to authorize a necropsy may in general be taken for granted, laws have been enacted in certain states which seem to limit the right of authorization for such examination, or which make specific requirements regarding such authorization, or which make postmortem examination mandatory in certain cases. A number of states require necropsy of executed criminals; in Hawaii, there is the interesting regulation that the high sheriff shall deliver the body of an executed criminal "to any surgeon who may wish to have such a body for dissection." The law of Connecticut specifies that the consent for necropsy of patients who die in hospitals must be in writing, and that hospital authorities may authorize an autopsy if, after due diligence, they cannot locate any relatives or friends entitled to the custody of the body, but provides further that the autopsy shall not be done until a reasonable time, not exceeding forty-eight hours, has elapsed. The Illinois statute contains an anomalous provision that has led some coroners to contend that a necropsy may not be held in that state unless authorized by the coroner, even if those legally entitled to give permission for the performance of an autopsy wish such an examination made. This contention is based on the final sentence of chapter 31, section 10, of the Revised Statutes of Illinois, which reads as follows:

In any case where a person is supposed to have come to his or her death by violence of a criminal character as aforesaid, and in cases where the cause of death is not known, and concerning which the circumstances evidence violence of a criminal character, or death from criminal means, or where said cause of death is unascertainable otherwise than by autopsy, the coroner may, in his discretion, either before or after the jury is summoned and sworn, call a physician to examine the body of the deceased, and if from examination, or from a preliminary investigation by the coroner, the cause of death cannot be definitely ascertained by the coroner, he may in his discretion, or the jury after being summoned and sworn, may, in its discretion, order and direct an autopsy to be held upon the body to ascertain the cause of death. . . . In all cases where the coroner has reasonable ground to believe or suspect, or where there is any evidence, that death resulted through criminal means or agencies, it shall be his duty to conduct a postmortem examination upon the body. *Provided*, however, that there shall be no autopsy ordered, directed or held except as heretofore in this section expressly provided.

It will be noted that the foregoing statute defines the conditions under which the coroner may perform or order an autopsy, and that it gives him wide authority in this respect. The two clauses that read "in cases where the cause of death is not known" and "or where said cause of death is unascertainable otherwise than by autopsy" would seem to give the coroner unlimited latitude in the matter of postmortem examinations. The final provision of the section, which states very clearly that a necropsy shall not be held except as provided in the rest of the section, which relates entirely and only to the authority of the coroner in such matters, would appear to prohibit the performance of an autopsy, even if consent has been given by surviving relatives, unless the coroner also authorizes the examination. If a suit brought against a coroner, ostensibly to limit his powers, should result in a decision upholding the constitutionality of the section as a whole, there will arise the possibility of interference with postmortem examination by an unfriendly coroner or undertaker, as well as the further possibility of a suit for damages if an autopsy is held with the consent of the relatives but without the express consent of the coroner. The Illinois statute leads one to feel that the laws of each state relating to the powers of the coroner should receive closer scrutiny by those interested in the development of medical science through postmortem examination than such laws have received.

In Louisiana, in addition to the statutory provision authorizing the coroner to hold a necropsy whenever deemed necessary by him, there is a regulation of the state department of health that permits the board or any local health officer to order a postmortem examination of any person or animal dead of a suspected communicable disease.

In Massachusetts and some of the other New England states that have adopted the medical examiner system, the authority for ordering a medicolegal necropsy is vested in the legal arm of the government. Nominally, at least, the medical examiner functions when ordered so to do by the attorney general, the district attorney, the mayor or the selectmen. In Oregon the coroner acts on direction of the district attorney. In Maine, which has the medical examiner system, the statute requires that a necropsy held by the medical examiner be made in the presence of a physician and one other "discreet person."

The Michigan law relating to necropsies appears at first glance to be restrictive. It is, however, definitive rather than actually restrictive. After stating that "the right to dissect the dead body of a human being shall be limited to cases specifically provided by statute," the law goes on to say that an autopsy may be done when authorized by the coroner, or by direction or will of the deceased, or when consent is given by the next of kin or by the person charged with the burial of the body. The extent of the postmortem examination may be limited by the person

authorizing its performance. Another Michigan statute gives the Industrial Commission the authority to order an autopsy if such examination is considered necessary in the settlement of death claims. Still another section provides that every autopsy performed by a coroner shall be held at a public morgue; if there is no public morgue, then the necropsy must be done at the residence of the deceased.

North Dakota, Oklahoma and Oregon recognize the authority of the coroner to hold or order an autopsy, the right of the person entitled to custody of the body to give permission for necropsy and the power of the legislature to enact specific provisions relating to necropsies. South Dakota, in addition to similar general provisions, specifically authorizes the postmortem examination of those who die while under medical care in a charitable institution maintained by the state, provided the next of kin have apparently neglected or abandoned the inmate. Failure to have made inquiries concerning the inmate during a period of six months preceding his death is defined as neglect.

The ordinances of the City of Manila, in the Philippine Islands, give to sanitary inspectors the right to demand a necropsy if there is reason to believe that the cause of death is different from that stated in the certificate of death. The Administrative Code provides for the aid of the department of legal medicine of the College of Medicine of the University of the Philippines in any death the cause of which is not satisfactorily explained. This would appear to be a nearer approach to making available the services of a university department of legal medicine in work of the kind usually done by the coroner than that which prevails in any part of the continental United States.

ANATOMICAL ACTS

Laws regulating the disposal of unclaimed dead bodies have been enacted by all states except Arizona, Delaware, Florida, Idaho, Louisiana, Maryland, Montana, New Mexico, Nevada and Rhode Island. The purposes and restrictions of the anatomical acts, as they have been termed, are much the same in the various states that have such acts.

Dead human bodies to which the anatomical acts apply are those which would have to be buried at public expense. They are bodies that are not claimed by relatives or friends, who would have to bear the expense of burial. The agencies that have control of such bodies at the time of death are usually those charged with the care of the indigent or criminal. These agencies are specified in the Arkansas law as follows: "the board of health of any city, village or township, the mayor or common council of any city, and the officer or board having direction or control of any almshouse, prison, house of correction or jail." In California the agencies which may have control of the body

at the time of death are the "sheriff, coroner, keeper of a city poor-house or reformatory, public hospital or asylum, county jail, State prison, or city or county undertaker, or any and all State, county, town and city officers having possession, charge or control of bodies to be buried at public expense." This state has the further interesting provision that if a body becomes "unfit" for educational purposes through neglect of the responsible person promptly to notify the board that he has such a body in his possession, the body is to be buried at the expense of the negligent official.

Practically every state that has an anatomic law exempts the bodies of travelers and strangers from the provisions of the law. In the Philippines the law does not apply to the bodies of prisoners. In most states, the disposal provided for by the anatomical act is not effective if the deceased has requested during his last illness that his body be buried. The Tennessee law does not apply to counties with a population of 4,000 or under. The unclaimed bodies of those dead of contagious disease do not come under the provisions of the anatomical acts of most of the states.

Some of the acts specify a period of forty-eight hours following death during which the body may be claimed by relatives or friends for burial. Other states require that immediate notification be given by telegraph to the authority that has control of unclaimed bodies. In Alabama, notice of the death of a supposedly friendless and destitute person must be posted on the door of the courthouse for forty-eight hours following death. Most states specify a period of time, which varies from twelve to sixty days, during which the body must be held by the final recipient before it may be used for the purposes stated in the act. If, during this period, the body is claimed by any one who is willing to defray the cost of burial, it must be surrendered without question.

Bodies, the disposal of which is covered by the anatomical acts, are in many instances those of persons on whom the superintendent or other administrative official of a hospital could, under the common law, grant permission for necropsy. As the acts abrogate this right, the pathologists may be inclined to feel a certain degree of hostility toward them. The legal custodian of the body under the act may, however, grant permission for postmortem examination if the latter is deemed necessary or advisable.

Without such authorization, pathology has precedence over anatomy in a few instances. The act of Georgia specifically states that autopsies may be done on the bodies of patients who die in the Georgia State Sanitarium. The Augusta State Hospital and the Bangor State Hospital of Maine need not surrender bodies to the anatomical board, but may themselves conduct autopsies, postmortem examinations and dis-

sections "for the advancement of medical science." Massachusetts also gives precedence to the autopsy, if the cause of death cannot be otherwise ascertained. New York recognizes the right of the person in charge of a hospital to order a necropsy, unless objection is made by the next of kin; in the case of unclaimed bodies, however, the medical schools have a prior claim on such bodies for the purpose of teaching anatomy.

The purpose of the anatomical acts is usually stated to be the advancement of "medical science," "anatomic science," "medical knowledge" or "medical teaching." They furnish material for the dissecting room. In so doing, they have wiped out the scandals of grave robbery and of the illegal sale and transportation of dead human bodies. The latter purpose is recognized in the act of the District of Columbia, which is entitled "An Act for the Promotion of Anatomical Science and to Prevent the Desecration of Graves in the District of Columbia." All of the anatomical acts provide that the body must be used within the state in which death occurred. Sale or transportation outside the state is punishable by fine or imprisonment or both. On the other hand, interference with the provisions of the act is also punishable.

The agency provided by the anatomical act for carrying out the provisions of the latter varies in different states, but is much the same in general principles. This agency becomes the legal custodian of the unclaimed dead body and makes distribution of such bodies in accordance with regulations named in the act itself or drawn up by the agency. The latter may be the state board of health, an anatomical board provided for by the act or named by the deans of the medical schools of the state, or the state or some other university.

The final distribution of bodies the disposal of which is provided for by the anatomical acts is, in general, to medical schools. The distribution is made according to the number of students enrolled. The Connecticut law specifically names the school of medicine of Yale University the recipient of unclaimed bodies. In Michigan, the act provides that the bodies of those who die outside the limits of Wayne County shall go to the University of Michigan; the Detroit College of Medicine and the Detroit Homeopathic College are made the recipients of the bodies of those who die within Wayne County. The University of Wisconsin receives the bodies from the western United States judicial district of the state, Marquette University those from the eastern federal judicial district. Mississippi, South Dakota, Utah and West Virginia name the state university in their acts.

Iowa gives recognition to osteopathy and chiropractic schools in the following:

The body . . . shall be delivered to the medical college of the State university or some osteopathic or chiropractic college or school located in this State,

which has been approved under the law regulating the practice of osteopathy or chiropractic.

In some states, schools of dentistry may receive bodies. Kansas, North Carolina and Virginia grant to schools for the teaching of embalming the same privileges as to medical schools.

Alabama, Illinois, New Hampshire, North Dakota, Pennsylvania, South Carolina, Vermont and Washington permit distribution of dead bodies to individual physicians and surgeons and to associations other than medical colleges. In most of these states the medical schools have the prior claim, individual physicians receiving bodies only if there is a surplus above the needs of the schools. In New Jersey, the official who has charge of an unclaimed dead body is required to give notice to the pathologic and anatomical associations of the county, and to surrender the body to either or both of these associations on request.

Some states, especially those that require that the body be held for a considerable time before it is used for dissection, require that the body be embalmed. Other states make no mention of embalming. All demand that the portions left after dissection be interred, cremated or disposed of in such manner as will not outrage public decency. In some states an approved bond must be filed before a body may be received by a school or a person.

EVIDENCE AND THE QUESTION OF PRIVILEGE IN RELATION TO THE DEAD BODY

Information gained by a physician from another person, when the relationship between the two is that of physician and patient, is privileged and as a general rule is not admissible as evidence. Although the common law does not recognize the privileged character of communications between physician and patient, many states have enacted statutes that prohibit a physician from divulging information gained by the treatment of a patient or through communications made by the latter. The federal courts also recognize the rule of privileged communications.

As a general rule, information gained by the performance of a necropsy is not privileged and is therefore admissible as evidence. A state of confidentiality, which is the basic principle that makes communications privileged, cannot exist between a dead body and a living person. A court decision⁹ expresses the matter thus:

A dead man is not a "patient," capable of sustaining the relation of confidence toward his physician which is the foundation of the rule given in the statute, but is a mere piece of senseless clay which has passed beyond the reach of human prescription, medical or otherwise.

9. *Harrison v. Sutter State Railway Company*, 116 (Calif.) 156.

The claim of privilege has a number of times been set up in court actions, with the object of preventing the admission as evidence of information gained by postmortem examination. Courts have consistently refused to allow the claim, and have admitted as testimony facts learned at necropsy.

In at least one instance,¹⁰ information gained through postmortem examination has been held inadmissible as evidence on the ground that it was privileged. In this case, the autopsy was done by the physician who had attended the deceased during her last illness. The court held that the physician's attendance on and treatment of the deceased during her lifetime had materially aided him in the performance of the autopsy and in the determination of the cause of death.

LIABILITY FOR UNAUTHORIZED NECROPSY

It has been noted in a previous section that necropsies may be done only when consent thereto has been given by those entitled to the custody of the body or charged with the duty of its burial, or when ordered by the coroner, or when made necessary by specific statutory enactment. An autopsy done under any other conditions is unauthorized and renders him who performs it liable to suit for damages.

In determining the liability for and the amount of damages, several important questions enter into consideration. Since there exists no right of property in the dead human body, it has been maintained by some that no property damage is done in the performance of an unauthorized autopsy. There does exist, however, a right of custody to the dead body, as well as a right or duty of sepulture. An essential element of these rights is possession of the body in the same condition it was in when the breath of life left it. Interference with or violation of these rights is a wrong or injury, for which the injured person may go to court. It is in their decisions on this subject that learned judges make frequent use of "mutilation," "desecration" and other opprobrious terms. Courts have been unanimous in the opinion that a person wronged by an unauthorized postmortem examination of a body, to the custody of which he is entitled, shall be compensated.

A question that appears to be in an unsettled state relates to the liability of the physician who does an unauthorized necropsy because he considers such an examination necessary to ascertain the cause of death, in order to be able to comply with the regulations concerning death certificates and burial permits. In one of the citations given by Weinmann,¹¹ the claim for damages was upheld. In other cited cases, courts have ruled that such an autopsy does not render the physician liable to damages if it has been done in a proper manner. Having a

10. *Thomas v. Township of Byron*, 168 (Mich.) 593.

11. Weinmann (footnote 2, p. 88).

bearing on this matter of unauthorized autopsies, is the ruling that the making of a slight incision for the purpose of determining the cause of death, there being no dismemberment or removal of organs, is not mutilation of the dead body in a sense that gives cause for legal action.

When an unauthorized autopsy is done for the avowed purpose of determining the cause of death, in order that the death certificate may be properly made out, the decision of the courts of any given state would probably be influenced by the statutory and departmental regulations governing death certificates and burial permits. If a physician honestly feels himself unable to state the cause of death, probably the safest course for him to pursue is to place on the coroner or medical examiner the responsibility of authorizing the certificate of death or a necropsy if the latter is necessary.

The removal of parts or organs from the body, consent for necropsy having been given in proper form, has also engaged the attention of the courts. Most pathologists and hospital administrators probably believe that when no verbal or written restrictions are included in the consent for necropsy, the latter may be as complete and as thorough as the pathologist deems necessary. In the first place, it is to be noted that the person entitled to give permission for necropsy is entirely within his rights in placing on the necropsy whatever restrictions he chooses. Any violation of the restrictions would be cause for legal action. Furthermore, it has been held that, an autopsy having been authorized, the doing of anything more than is actually necessary to determine the cause of death is not permissible. Weinmann¹² said that a "physician cannot legally remove and retain portions of the body, unless such procedure is essential for determining the cause of death or for the determination of some other reason for which the autopsy was ordered or permitted." In a case¹³ in which a father alleged that organs had been removed from the body of his son during an autopsy and had been illegally retained or disposed of, the court made the following strong statement:

While it may be true there is no right of property in a dead body, in the ordinary sense, it is also true that the nearest relatives of the deceased are and always have been in all ages, so far as known, except under ecclesiastical law, recognized as legally entitled to its custody, to lay it away in burial. It is the duty no less than the right of such relatives to protect it from unnecessary violation, and any infringement upon that right, except where made necessary for the discovery and punishment of crime, violates the tenderest sentiments of humanity. . . . Unless sufficient reason existed for an autopsy he was entitled to the body un mutilated. If such reason did exist, he was, nevertheless, entitled to the whole body, even though necessarily disfigured, unless it proved necessary to remove and preserve some particular organ for further

12. Weinmann (footnote 2, p. 90).

13. Palenzke v. Bruning et al., 98 (Ill.) A. 644.

examination, as to whether a crime had been committed, or for evidence. But none—coroner, nor doctor, nor undertaker—had the right to remove parts of the body and, without the parents' consent, throw them into a privy vault. Such conduct violates every instinct of propriety, and could not fail to outrage the feelings of kindred of the deceased. For such violation of appellant's rights an action for damages can, we think, be maintained.

The attitude of the legal mind toward postmortem examination and the fine distinctions it draws between the act, the intent and the letter of the law are not always entirely or easily comprehensible. Judges speak of the determination of the "exact cause of death" as if this were an exact science, or as if it could be done by means of a small incision or by superficial inspection of the organs through a larger incision. Every pathologist knows that the cause of death must often be determined by exclusion, by the careful examination of every important organ of the body in order that he may decide that any given lesion is the cause of death. He knows that he must frequently call to his aid every resource of pathologic histology, chemistry and bacteriology to determine the cause of death. His defense, if accused of carrying a post-mortem examination further than may seem necessary or of retaining anything from the body, would probably be that he alone is competent to decide what is necessary to do in order to determine the cause of death in anything approaching the exact manner that the law seems to recognize.

A final point for consideration is the responsibility of the pathologist who permits any one to witness a postmortem examination. The embalming laws of a number of states, which are discussed in a later section, specifically prohibit the presence of any one during the preparation of a dead body other than those actually necessary for the work. It has been held that the right of privacy, even when such right is recognized, dies with the individual. Yet in the matter of permitting any one to be present at an autopsy, there enters again the question of the feelings of surviving relatives. Whether a pathologist lays himself open to a claim for damages if he permits witnesses at a necropsy, other than a medicolegal one, in which case the presence of witnesses may be required by law, has not come up for adjudication. In the absence of legal precedent, Weinmann¹⁴ gave the following opinion:

It would appear that if the conduct of a person who introduces total strangers into an autopsy room is of such a character as to arouse a feeling of repulsion toward the perpetrator of the act on the part of the next of kin or other relatives or friends; if such action would tend to subject the relatives or kindred to ridicule or unpleasant notoriety; or if such act would be reasonably certain to shock the sensibilities of any person, it would seem reasonably certain that such an act would render the person guilty of it liable in an action for damages.

14. Weinmann (footnote 2, p. 91).

It will be seen that he whose duty and work it is to make postmortem examinations exposes himself to the possibility of legal action, if the examination is unauthorized or if certain other contingencies arise in the course of an autopsy for which consent has been given. If the action is a claim for damages, its basis is not a violation of a right of property in the dead body, but a violation of the rights of custody and sepulture, with resulting mental anguish and injury to the feelings of those who have these rights. Mention has already been made of the doctrine of mental pain and anguish. In its relation to unauthorized autopsies, Weinmann¹⁴ discussed it again as follows:

We have already seen that damages for mental pain and anguish have been awarded in cases involving the question of a violation of the rights of sepulture vested in the legal custodians of the body. This same rule holds good in cases of unauthorized autopsies. It will not be necessary to go into the theory of "mental pain and suffering" as that has been done to an extent sufficient for our purposes in a preceding section.

Suffice it to say, that in those jurisdictions allowing damages for injuries to the feelings, a pathologist who performs an unauthorized autopsy, will render himself liable in damages to the extent of being compelled to pay for the damage he has inflicted on the feelings of the persons injured. In jurisdictions which will not allow damages for mental anguish in a case like the one under discussion, the great probability is that merely nominal damages could be collected, for the only theory on which damages are ordinarily assessed is a violation of a right of property. Now we know that no one has a right of property in a dead human body, and therefore the pathologist who performs an autopsy without the consent requisite to make it a valid act, violates no right of property. Therefore, if the court will not allow damages for mental suffering, it would follow that only nominal damages could be awarded. It would be safe to say, however, that in the great majority of cases a person making an unauthorized autopsy would render himself liable to pay for such injury to the feelings—or exemplary damages, as some courts have put it who do not wish to say that they have allowed damages for mental anguish in such a case.

EMBALMING

In most of the states, regulations relating to embalming deal with licensure of embalmers. Some states have statutory or departmental provisions that are of interest to the pathologist, the medicolegal expert or the public health official, in that they make embalming mandatory in certain cases, prohibit it in certain others or prescribe the ingredients of the material used for embalming.

Colorado, Connecticut, Illinois, Kansas, Maine, Massachusetts, New Jersey, New Mexico, Oklahoma, South Carolina, Vermont, Virginia, Wisconsin, Wyoming, the District of Columbia, the Philippines and Porto Rico prohibit embalming if there is reason to believe that death was due to other than natural causes, unless permission is obtained from the coroner, medical examiner or other proper official. The

wording of the statutes of many of these states is such as to appear to place the responsibility of determining whether permission for embalming is necessary directly on the undertaker or embalmer. If a certificate of death is required before embalming in any case, the undertaker is relieved of the responsibility of determining whether the circumstances of death were such as to require permission.

The composition of the embalming material, especially as it relates to interdicted substances, is covered by regulation in Connecticut, Idaho, Kansas, Mississippi, Nebraska, New Hampshire, South Dakota and Wyoming. The substances most widely prohibited are mineral poisons, of which arsenic and mercury are named in most instances. Some states add zinc, lead, copper, silver or antimony to the list. Since the law is such a stickler for verbal precision, one wonders what an embalming fluid might contain in Mississippi, where such a fluid may not contain "arsenic or other deadly poisons." Chloral, strychnine or cyanogen compounds are not permitted in some states. In certain states, only fluids containing formaldehyde may be used. A statement on the label giving the percentage of formaldehyde, or one indicating that the fluid contains no mineral poisons, may be required. The amount of fluid to be used may be specified; this is usually 5 per cent of the body weight in ordinary cases, and 10 per cent in contagious diseases.

Delaware specifies a long list of contagious diseases in which embalming must be done before the body may be removed from the room in which death occurred. This state also requires that when death was due to smallpox, the body must be "cremated or buried deep." In New York, "before embalming any dead body, or injecting therein any fluid, such tests as shall be prescribed by the supervisor of embalming must be applied, to determine beyond all doubt the fact that life is extinct." In the District of Columbia a body may not be embalmed within four hours of death, unless a certificate of death has been filed and accepted before the expiration of this period. In Arizona and Nebraska, none other than the embalmer and his absolutely necessary assistants may be present in the room where a body is being embalmed or prepared for burial. In the Philippines, "all embalming must be performed only in a morgue properly built so that it is free from flies and other insects."

TRANSPORTATION OF THE DEAD BODY

Regulation of the transportation of the dead human body is delegated in most states to the department of public health or some other similar agency. In addition to such regulations, the transportation is governed also by rules made by the common carrier and by the federal quarantine and customs regulations. In general, transportation requires a transit permit originating at the place where death occurred. A

permit issued by the state into which the body is to be shipped is also required by certain states. A prerequisite for the transit permit is an accepted certificate of death, the issuance of which covers any matters that may concern the coroner, medical examiner, registrar of vital statistics or public health officials.

Other details vary considerably in the different states. The regulations in force in Arizona have been adopted by the National Funeral Directors' Association. The main features of the Arizona regulations are covered in one form or another by the rules of most other states.

When death has been due to certain specified contagious diseases, namely, smallpox, plague, Asiatic cholera, typhoid, scarlet fever or diphtheria, the body must be thoroughly embalmed with an approved fluid and must be placed in an hermetically sealed metal or metal lined box. In deaths due to other causes, embalming may not be required if the body can reach its destination within twenty-four hours after death. If a longer period is required, embalming is necessary.

The size of the body box, the number of handles that it must have and the transit labels to be affixed are often specified. Many states prohibit the shipment with the body of articles that may have been exposed to contagion during the course of a contagious disease. Persons who have been exposed to such diseases may not accompany the dead body under the rules of certain states.

BURIAL

The usual method of final disposal of the dead human body, other than the methods prescribed by anatomical acts in the case of unclaimed dead, is burial. Under the common law it would probably be legal to bury a body in any place determined on by the next of kin, on whom the duty of sepulture devolves. The right of burial in a place requested by the deceased or determined on by the next of kin would no doubt be restricted, even under the common law, by regard for public health and public sentiment. The legality of interment in places other than recognized burial grounds has usually come to the attention of the courts in the case of infants and children who have been buried by parents who claimed that they could not meet the expense of regular burial or that the recognized burial place was inaccessible. Questions other than burial, such as infanticide or failure to have filed a certificate of death, may enter into such cases.

What might be legally done under the common law is restricted by the statutory regulations in force in all states relative to the disposal of the dead. What may be done is influenced first of all by the necessity of filing a death certificate signed by the attending physician, or by the health officer, registrar of vital statistics, coroner or medical examiner if death occurred without medical attendance. Filing of the

certificate of death necessitates the obtaining of a burial, disposal or removal permit. The regulations concerning the latter usually specify the length of time that the body may remain unburied and the place and manner of its interment.

CREMATION

Cremation is one of the most ancient forms of disposal of the dead. With the advent of the Christian era it fell into disuse, to come into favor again only comparatively recently. The paucity of definite regulations relating to this form of disposal is ascribed to its relatively recent revival. In general, it would appear that if there are no definite legal provisions regulating the procedure, conformity with the regulations for burial will permit cremation.

California, Colorado and Pennsylvania by statute require special permits for cremation. Connecticut, Missouri, New Jersey and Ohio have regulations relating more especially to the location and management of crematories, the records to be kept or the disposition that may be made of the ashes. Minnesota, New York and Nevada have statutes that make burial and cremation alternative methods of disposal. Although these are the only states mentioned as having regulations regarding cremation, in many other states the permission of the coroner or medical examiner is necessary before a body may be cremated. The purpose of such a rule is the wise one of preventing the destruction of necessary evidence if circumstances should make necessary an inquest or an investigation of the death.

The brief section on cremation closes with the following interesting paragraph:¹⁵

Whether special regulations concerning cremation exist in a given jurisdiction or not, it is essential, when cremations are made, to secure the burial permit, etc. Even when a physician cremates the body of a stillborn child, when it has advanced to that stage of development when it can be said to be a human body, or when he burns a portion of a body removed during the course of operation (if that portion of a body is considered as a dead body in his particular jurisdiction), it is essential that all certificates be filed, permits obtained, and returns and reports be filed as required by law in case of interment, if no specific regulation concerning cremation exists.

EXHUMATION

Most of the common law court decisions on the subject of exhumation relate to controversies between surviving relatives over the removal of a body that has been buried. Exhumation in such cases has no medicolegal interest. Such an interest is involved, however, if the exhumation is for the purpose of determining the cause of death in

15. Weinmann (footnote 2, p. 178).

order to establish or to disprove a claim for insurance. Courts usually refuse to order exhumation unless some controlling public reason or superior private right is involved.

But the matter of exhumation is not entirely one of common law. In many states it is covered by statute or by the regulations of the department of health. The coroner or medical examiner may authorize exhumation, if there have come to light after the burial of the body, circumstances that make examination of the body advisable from the standpoint of criminal justice.

The statutory or departmental regulations of most states in regard to exhumation have for their chief purpose the protection of the public health. With this object in view, the rules laid down relate to the time of day or year when exhumation may be done, or they prohibit the presence of any persons other than those necessary for the work. Some states require a special permit from the department of health, the department of public welfare or the bureau of vital statistics. Some require special permits for disinterment only when death was due to certain specified infectious diseases. In such cases there may be prescribed a minimum period of time that must elapse between death and exhumation.

The subject of exhumation is briefly summarized by Weinmann thus:¹⁶

Although courts are loath to disturb a corpse in its final resting place, yet exhumation will be ordered when required by the demands of justice and equity. In all such cases, however, there must be a strong showing of some controlling public reason or superior private right; and due regard will always be given to the wishes of the decedent expressed during his lifetime, when possible; to considerations of public sentiment, public health, and public welfare, generally; and finally, to the feelings of surviving relatives and friends.

CONCLUSION

An attempt has been made to summarize the information contained in "A Survey of the Law Concerning Dead Human Bodies." For most of the subjects covered, the original bulletin quotes in detail the laws of the various jurisdictions, which are arranged alphabetically according to states and territories. The reader who desires more detailed information of the law on any particular subject in any given jurisdiction is referred to the original. It should be borne in mind that the laws as given may be modified by additional local municipal regulations.

16. Weinmann (footnote 2, p. 192).

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—

The University of Pennsylvania has conferred the honorary degree of doctor of laws on Theobald Smith, who recently retired as director of the department of animal pathology at Princeton of the Rockefeller Institute for Medical Research.

Matthias Nicoll, Jr., has resigned as commissioner of health for the state of New York to become health officer of Westchester County, N. Y.

Thomas Parran, Jr., of the U. S. Public Health Service has been appointed commissioner of health for the state of New York.

Viktor Müller-Hess, professor of legal and social medicine in the University of Bonn, has been appointed professor of legal medicine in the University of Berlin in the place of Fritz Strassmann.

Dr. Kenneth M. Lynch, professor of pathology, Medical College of the State of South Carolina, was elected president of the South Carolina Medical Association at its eighty-second annual convention, May 6 to 8. Dr. Lynch is also serving this year as president of the American Society of Tropical Medicine and as president-elect of the American Society of Clinical Pathologists.

Medical Fellowship Board of National Research Council.—The next meeting of this board will be held on Oct. 14, 1930. Applications for consideration at this meeting must be in the hands of the secretary of the board (B and 21st Streets, Washington, D. C.) before September first next.

Charles Nicolle, director of the Pasteur Institute of Tunis, and well known for his work on typhus fever for which he was awarded a Nobel Prize in 1928, has been elected a member of the French Academy of Sciences.

At the recent meeting in Atlantic City of the Association of American Physicians, the Kober Medal was awarded to James B. Herrick, Chicago, for his investigations in clinical medicine.

George R. Minot, Boston, has been awarded a gold medal by the National Institute of Social Sciences, New York.

The Trudeau Medal of the National Tuberculosis Association has been awarded to Henry Sewall, Denver, in recognition of his work on tuberculosis.

H. J. B. Fry, pathologist to the Research Institute, Cancer Hospital, London, died on May 5, 1930, from streptococcal infection contracted while making a postmortem examination.

American Association of Pathologists and Bacteriologists.—At the meeting in New York, April 17 and 18, 1930, the following officers were elected: president, George R. Callender; vice-president, Ward J. MacNeal; treasurer, F. B. Mallory; secretary, Howard T. Karsner; incoming member of council, O. T. Avery; assistant secretary, Robert A. Moore.

For distinguished service in pathology and bacteriology, the Gold Headed Cane of the Association was conferred upon Theobald Smith, Princeton, N. J.

Committee on Research in Syphilis.—It is reported (Venereal Disease Information 11:63, 1930) that this committee now sponsors four major groups of studies: the biology of *Spirochaeta pallida* (cultivation, life cycles, different strains, relation between syphilis and yaws); the reaction of the body to syphilitic infection (latent infection, reaction to infection and to antisyphilitic drugs, mechanism of Kahn and Hinton tests); experimental chemotherapy; relation of treatment to the development of dementia paralytica. For these purposes, twenty grants have been made, amounting in all to \$91,515. In addition, funds have been provided for the study of the results of treatment for syphilis, and for other special objects.

German Society for Legal and Social Medicine.—The society has a membership of about 400 and publishes the *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*.

International Congress of Veterinary Medicine.—The Eleventh International Congress on Veterinary Medicine will be held in London, England, Aug. 4 to 9, 1930. The General secretary is F. Bullock, LL.D., F.C.I.S., 10 Red Lion Square, London, W. C. 1.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE R-T INTERVAL IN MYOCARDIAL INFARCTION. A. R. BARNES and M. B. WHITTEN, *Am. Heart J.* 5:142, 1929.

In the left ventricle the branches of both the right and the left coronary arteries are similar in architecture, leaving the main artery at right angles and directly penetrating the myocardium. In the right ventricle the branches of the right coronary artery leave it in the same general direction as that of the vessel from which they arise. Myocardial infarction of the right ventricle is rare. Infarction from occlusion in the right coronary circuit is almost always found in the posterior portion of the left ventricle and septum, and at times in the apex. Occlusion of the left coronary artery usually involves some part of the anterior portion of the left ventricle and septum. Infarcts in these various locations produce characteristic changes in the R-T interval, which enable one not only to localize the region involved but also often to identify the coronary artery that is the seat of the trouble.

PEARL ZEEK.

THE AGE AND SEX INCIDENCE OF ARTERIAL HYPERTENSION. J. E. F. RISEMAN and SOMA WEISS, *Am. Heart J.* 5:172, 1929.

The curve of age incidence in patients with hypertension shows a gradual progressive rise up to the age at which begins the involution of the male and female glands of internal secretion. At this point there is a sharp sudden rise. More than 60 per cent of the cases occur in patients between the ages of 45 and 69. These facts suggest the possibility of an etiologic relationship between involutional changes of the human body and hypertension.

PEARL ZEEK.

LYMPHATIC ABSORPTION OF PARTICULATE MATTER THROUGH THE NORMAL AND THE PARALYZED DIAPHRAGM. W. S. LEMON and G. M. HIGGINS, *Am. J. M. Sc.* 178:536, 1929.

Experiments on absorption through the normal and the paralyzed diaphragm confirm the observations made by Higgins and Graham that five main channels carry particulate matter from the peritoneum upward through the thorax and into the blood stream. The experiments also demonstrate the presence of a descending thoracic vessel which passes downward over the posterior wall of the thorax, sometimes receiving tributaries from the vessels of the posterior portion of the diaphragm and communicating with the lymph nodes in the region of the kidney. The particulate matter seems to be taken up diffusely on the under surface of the diaphragm. The transfer from the peritoneal surface to the pleural surface is rapid, and the penetration of particulate matter into the blood stream is effected within a period of from thirty minutes to one and a half hours. The material taken from the lymphatic vessels on the surface of the diaphragm is mainly found in a free state, although a small amount is in phagocytic cells. That taken from the lymph nodes is found mainly in phagocytic cells, although a slight amount is still in a free state. When obtained from the blood the material is both in a free state and within phagocytic cells. It is probable that the monocytes take up the free material quickly after it has been passed into the blood stream. There is no question but that normal muscular contraction of the diaphragm contributes much to the passage of the particulate matter. Nevertheless the difference in size of the lymphatics on the two leaves of the diaphragm is

also important. The lymphatics on the right side are much larger and carry a much greater proportion of the lymphatic flow than those on the left. Even after paralysis of the right half of the diaphragm, the pattern discovered following the lapse of thirty minutes is more distinct than on the normal left side. Absorption through the left half when it is paralyzed is insignificant.

JOHN PHAIR.

INTRACRANIAL PRESSURE IN MAN DURING SLEEP AND UNDER CERTAIN OTHER CONDITIONS. LEWIS STEVENSON, B. E. CHRISTENSEN and S. BERNARD WORTIS, *Am. J. M. Sc.* **178**:663, 1929.

1. Intracranial pressure is increased during sleep. The pressure gradually rises until the patient is sound asleep, when the curve reaches its maximum; this is maintained at a fairly constant level during sound sleep. On awakening, the pressure falls rather rapidly again to normal.

2. There is an increase of the intracranial pressure on lying down.

3. Partial sleep or drowsy states are associated with a rhythmic increase of the intracranial pressure which is not so high as during sound sleep.

4. Certain drugs which are known to affect the nervous system as sedatives or as stimulants depend in part for their effect on a hitherto unappreciated mechanical factor, namely, an increase or a decrease of the intracranial pressure. For example, morphine, a sedative, causes an increase of the intracranial pressure, while caffeine, a stimulant, produces a fall.

5. The intracranial pressure is, within wide limits, independent of the blood pressure.

6. The authors' conception of the physiology of sleep, arrived at from a study of their experiments and those of other workers, is as follows:

They believe that the sympathetic center in the brain which maintains vasomotor tone in the vessels becomes periodically fatigued. This results in a vasodilatation of the blood vessels of the brain, as well as those of the periphery. Accompanying this, as further evidence of fatigue in the sympathetic system during sleep, are the constricted pupil, the slower heart rate and the decrease of blood pressure. This vasodilatation in the brain would result in one of two things:

1. The brain volume would be increased with a consequent pulling apart of the neurons (diaschisis). This might result in a physiologic interruption of function in the manner suggested by Cajal and Duval when they assumed that the dendrites of the nerve cell were contractile.

2. The pressure of the cerebrospinal fluid within the brain would be increased and especially in the pericellular spaces, thus altering the conductivity of the synapse.

AUTHORS' SUMMARY.

DIABETES INSIPIDUS AND LESIONS OF THE MIDBRAIN. T. B. FUTCHER, *Am. J. M. Sc.* **178**:837, 1929.

A case of diabetes insipidus due to an alveolar carcinoma of the hypothalamus, secondary to a primary carcinoma of the lung, and without involvement of the pituitary, is reported. The case would naturally tend to support the view held by many that the diabetes insipidus is due to disturbance of certain regulatory centers in the hypothalamus. The studies supporting the pituitary and hypothalamic conception of the origin of the disease are reviewed. Reference is made to the fact that it now seems amply demonstrated that there are definite nerve fibers connecting the tuber cinereum and the posterior lobe of the hypophysis. The belief is expressed that, although there may be certain centers in the hypothalamus regulating water exchange in the body, the evidence seems strong that disturbance of the action of a diuretic-antidiuretic hormone produced in the posterior lobe of the pituitary is an important factor in the etiology of the disease, possibly by sensitizing these centers or by influencing their function.

AUTHOR'S SUMMARY.

MECHANISM OF OVULATION IN THE RABBIT. M. H. FRIEDMAN, *Am. J. Physiol.* **90**:617, 1929.

While no effect was observed on ovulation in the rabbit by the transplantation or injection of rat hypophysis, the intraperitoneal injection of the urine of pregnant women produced luteinization of the corpora hemorrhagica of the ovary of the rabbit, and a single injection provoked ovulation. Urine from nonpregnant women was without this effect.

H. E. EGGERS.

PRODUCTION OF ARTIFICIAL DECIDUOMA WITH EXTRACTS OF THE CORPUS LUTEUM. L. A. GOLDSTEIN and A. J. TATELBAUM, *Am. J. Physiol.* **91**:14, 1929.

The writers' experiments confirm the observation that in corpus luteum extract there is a special hormone which as one of its functions, so sensitizes the uterine mucosa in the guinea-pig that deciduoma is formed on indifferent stimulation of the endometrium at the proper period of the sexual cycle.

H. E. EGGERS.

THE EYE IN DIABETES MELLITUS. MARTIN COHEN, *Arch. Ophth.* **2**:529, 1929.

Diabetes usually occurs in middle life when arteriosclerosis is apt to be present. But the ocular complications appear after the disease has continued for some years, and the patient is debilitated, susceptible to infections, or chronic disorders have set in. Of all eye lesions associated with diabetes, the incidence of retinitis is highest; cataract, chronic retrobulbar neuritis, muscular disorders and disturbances of accommodation, refraction and iritis occur more rarely.

The structure of the eye most frequently involved in diabetes is the retina, primarily its vessels, the most typical example being lipemia retinalis, which involves both eyes and occurs in severe diabetes. In a case cited, all the retinal blood vessels were moderately dilated and had a milky appearance. This appearance alone, exclusive of any examination of blood or urine, determines the diagnosis of diabetes. Microscopically, the vascular walls were not involved in any case reported. This appearance of the fundus antedates coma by six weeks. The author believes that the appearance of lipemia retinalis is closely related to the total fat content of the blood rather than to the cholesterol.

Diabetic retinitis is usually bilateral. The retinal vessels often show definite pathologic evidence with varying degrees of arteriosclerosis. If general hypertension is present, it is apt to aggravate the lesion of the fundus. The author believes that this lesion is mainly due to sclerosis of the retinal vessels, which may be either mild or severe. The disturbed sugar metabolism is only contributory.

Cataract in young diabetic patients may exist from early childhood. In older persons it is probably the usual type of senile cataract complicating diabetes. Diabetic and senile cataracts cannot be differentiated by any known test. The author cites an instance of diabetic cataract developing in a child at the age of 1 year and 1 month.

In experiments with lenses of oxen, it is found that the fresh lens, when immersed in Ringer's solution and incubated, develops the power to convert dextrose into lactic acid. The same utilization occurs when the lenses are immersed in the aqueous humor, but there is no change if placed in the vitreous humor. This ability to utilize dextrose is apparently dependent on the presence of glutathione in the lens. In the diabetic person, the production of cataracts may be an expression of the general inability to utilize dextrose, and the lens therefore degenerates.

CHARLES WEISS.

THE REACTIONS OF SIMPLE GOITRE TO IODINE. BRUCE WEBSTER, *Bull. Johns Hopkins Hosp.* **45**:215, 1929.

Potassium iodide in quantities of 5, 2.5 and 1.25 mg. was injected intraperitoneally into rabbits with simple hyperplastic thyroid glands. The changes

in heat production were studied and correlated with the histologic changes produced in the gland, as determined by biopsy. The quantity of thyroid hormone elaborated, as indicated by changes in heat production, appeared to vary directly, within certain limits, with the amount of available iodine, as did the extent of involution produced in the gland. This relationship apparently held true until involution was nearly complete.

AUTHOR'S SUMMARY.

THE COLOR OF THE SKIN AS ANALYZED BY SPECTROPHOTOMETRIC METHODS.
C. SHEARD and LOUIS A. BRUNSTING, *J. Clin. Investigation* 7:559; 575; 593, 1929.

The fundamental hue or dominant wavelength of the skin lies in the spectral region 590 millimicrons (sodium yellow). The deposition of melanin in the skin from sunlight decreases its relative luminosity but does not disturb the hue or its purity. The same hue prevails in the white as in the so-called black, red and yellow races. The blood in the superficial capillaries exerts a major influence on the color of the skin.

CHANGES OF THE TRYPANOCIDAL PROPERTY OF SERUM IN PERNICIOUS ANEMIA.
F. ROSENTHAL, *Klin. Wchnschr.* 8:1436, 1929.

During periods of remission the trypanocidal property of the serum of patients with pernicious anemia diminishes. It increases with the return to normal of the blood. There is no satisfactory explanation for these changes, although they resemble those occurring in diffuse diseases of the liver.

EDWIN F. HIRSCH.

THE RESORPTIVE PROPERTY OF THE INTESTINAL WALL FOR H AND OH IONS.
K. SCHEER, *Klin. Wchnschr.* 8:1757, 1929.

About two hours after rectal injection of hydrochloric acid the urine becomes distinctly more acid, and about four hours after the rectal injection of sodium bicarbonate the urine becomes distinctly more alkaline. These results demonstrate that the mucosa of the colon is able to absorb H and OH ions.

EDWIN F. HIRSCH.

THE EFFECT OF AN EXTRACT OF THE ANTERIOR LOBE OF THE HYPOPHYSIS ON THE EXCRETION OF MILK. F. GRÜTER and P. STRICKER, *Klin. Wchnschr.* 8:2322, 1929.

A hormone of the anterior lobe of the hypophysis has a stimulating effect on the mammary glands. Probably at the time of birth it stimulates the secretion of milk. Extracts from the liver, the lungs, the posterior lobe of the hypophysis and even the placenta are without such effects.

AUTHORS' SUMMARY.

EFFECT OF NUTRITION ON THE BEGINNING OF PUBERTY AND THE OVARIAN CYCLE. W. NEUWEILER, *Ztschr. f. Geburtsh. u. Gynäk.* 94:28, 1928.

The date of the first estrum and the subsequent ovarian cycle of young female rats fed from the third week of life with different diets was determined by the method of Allen and Doisy. The diets used were: normal, rich in carbohydrates, rich in proteins, rich in fats, free from vitamins plus factor A, B, C, and E, respectively. With the normal diet, the first estrum appeared after from forty-two to forty-five days, and the normal ovarian cycle was from four to seven days. With all the other diets used, the animals could not be kept alive over a long period. All the animals of these groups were dead after one hundred and fifteen days. Degenerative changes of the sexual organs appeared in these animals at an earlier date than noticeable changes in their general status. No estrum was

seen in the great majority of animals fed with diets rich in fats or free from vitamins. In animals fed with the remaining diets, the beginning of the estrum was delayed for from one to three weeks. The ovarian cycle in animals fed with a diet rich in carbohydrates was from two to three weeks, in those with a diet rich in proteins, from twenty-two to twenty-four days. A second estrum, however, appeared in only a few of these animals. The diet free from vitamins plus factor A had a similar effect. Animals fed with diets free from vitamins plus factors B, C and E, respectively, had a delay of fourteen days of the first estrum. This condition then remained permanent either immediately following the first estrum (vitamin E), after a period of five days (vitamin C) or after fifteen days (vitamin B). The ovaries of all animals fed with pathologic diets showed a marked hypoplasia and severe degeneration of the follicles.

W. C. HUEPER.

PATHOGENESIS OF ICTERUS NEONATORUM. W. G. SCHULTZ, *Ztschr. f. Geburtsh. u. Gynäk.* **94**:793, 1929.

Erythrophagocytosis and considerable deposition of iron pigment in the reticulo-endothelial system of the spleen and liver are absent in fetuses until 4 or 6 months of age. They are present in mature and immature fetuses during delivery and increase in amount with the duration of the delivery and of the extra-uterine life. The common icterus neonatorum is considered as an expression of a hyper-function of the reticulo-endothelial system. The cause of it is unknown.

W. C. HUEPER.

Pathologic Anatomy

CONGENITAL HEART DISEASE. WINSTON F. HARRISON, *Am. Heart J.* **5**:213, 1929.

A clinicopathologic study was made of a case of congenital heart disease exhibiting the complex known as the "tetralogy of Fallot," on which was superimposed a subacute bacterial endocarditis with massive vegetations involving chiefly the tricuspid valve. Associated anomalies in both the heart itself (Chiari's network) and elsewhere are discussed with reference to their bearing on the theories of the etiology and pathogenesis of congenital cardiac defects. Special reference is made to the collateral pulmonary circulation in the presence of extreme pulmonary stenosis or atresia when the ductus arteriosus is closed. In such cases the enlarged bronchial arteries usually supply the blood to the lungs, although sometimes the pericardials, mediastinals, coronaries, esophageals, subclavians or other arteries are called on to assume this function. In the present case the bronchial arteries were greatly enlarged. Aspects of the pathologic physiology are discussed with reference to the degree of disturbance of the circulation and its relationship to prognosis. The danger from infections is noted particularly in the extraordinary forms of vegetative endocarditis to which such cases are especially prone. Most patients die from intercurrent diseases and not from cardiac failure.

AUTHOR'S SUMMARY.

PROGERIA: REVIEW OF THE LITERATURE WITH REPORT OF CASE. VINCENT T. CURTIN and HERMAN F. KOTZEN, *Am. J. Dis. Child.* **38**:993, 1929.

We have presented a case of what we believe to be a relatively rare disease. The possibility that this condition should be considered as scleroderma has been suggested. The characteristic facies, evident from a comparison of the photographs and commented on by Gilford and other observers, the changes in the cardiovascular and osseous systems, the similarity in the mentality of the persons affected, the subsequent course and termination, and the pathologic observations

in the cases coming to autopsy, seem sufficient to warrant its description as something more than dermatosclerosis. Neither can it be considered Still's disease, as the arthritis is but one of the many clinical manifestations. Whether or not we accept Gilford's name, progeria, or that of dwarfism of the senile type, proposed by Variot and Pironneau, we must certainly admit this morbid state to be a distinct entity. Failure to secure permission for a postmortem examination in the case of L. F. places any opinion as to the possible cause in the realm of speculation, although we feel that the arguments in favor of disease of the suprarenal gland have the most foundation in fact. Until more of these cases come to autopsy, however, we must remain in doubt as to the causative factor of what is clearly a most interesting disease.

AUTHORS' SUMMARY.

INTERPRETATION OF ROENTGENOGRAMS OF THE CHEST IN CHILDREN BASED ON OBSERVATION AT NECROPSY: TUBERCULOSIS. JOHN A. BIGLER, *Am. J. Dis. Child.* **38**:1166, 1929.

Evidence of tuberculosis is not found pathologically as frequently as one would expect from the diagnosis of films of the chest. The incidence of tuberculosis in children admitted to the Children's Memorial Hospital is much lower than the figures quoted for tuberculosis in children. The primary focus is found more often pathologically than on the x-ray film, unless calcification is present. The more or less characteristic hilar, or mediastinal shadow, is the most frequent guide to the diagnosis. Miliary tuberculosis can be recognized on the films in only about 50 per cent of the cases. It can be differentiated from chronic tuberculous bronchopneumonia by the smaller size of the shadows. Repeated tuberculin tests, when negative, are important in ruling out a diagnosis of tuberculosis.

AUTHOR'S SUMMARY.

ANOMALIES OF THE URINARY TRACT IN INFANTS. ALGERNON S. HURT, JR., *Am. J. Dis. Child.* **38**:1202, 1929.

In a series of 101 necropsies on infants less than 2 weeks of age, five cases were found in which there were anomalies of the urinary tract. Since these anomalies occurred in such a low age group, this percentage may be taken as at least an indication of the incidence of anomalies of the urinary tract at birth. Although the series reported is comparatively small, the data corroborate the evidence that anomalies of the urinary tract are by no means infrequent in infants and children.

AUTHOR'S SUMMARY.

SPLENOMEGALY: PORTAL PHLEBOSCLEROSIS. SAMPSON J. WILSON and MAX LEDERER, *Am. J. Dis. Child.* **38**:1231, 1929.

A case of portal phlebosclerosis in a boy, aged 2 years, due to a congenital stenosis, is described.

CONGENITAL ESSENTIAL THROMBOCYTOPENIA. HARRY M. GREENWALD and IRVING SHERMAN, *Am. J. Dis. Child.* **38**:1245, 1929.

A case of congenital thrombocytopenic purpura is reported. The reduction in the number of the platelets is attributed to an insufficiency of megakaryocytes of the bone-marrow. The coincidence of anomalies of the heart and of the thymus gland with defective formation of the megakaryocytes supports the conception of the congenital nature of the thrombocytopenic purpura.

AUTHORS' SUMMARY.

MIKULICZ'S DISEASE AND THE MIKULICZ SYNDROME. J. P. CROZER GRIFFITH, *Am. J. M. Sc.* **178**:853, 1929.

Two cases of Mikulicz' syndrome are reported; one dependent on leukemia, the other, which might be called Mikulicz' disease proper, having no discoverable

cause. The symptoms and lesions are discussed with special reference to the influence of tuberculosis. A study of some of the literature as well as the bioscopic examination in my own case supports the conclusions of others, viz., that although tuberculosis may be a cause of Mikulicz' disease, it is rarely so, and that even a histologic appearance in the glands which strongly suggest tuberculosis is not a positive proof that the disease is present.

AUTHOR'S SUMMARY.

THE FINER HISTOLOGY OF THE NORMAL GLOMERULUS. LEONE MCGREGOR, *Am. J. Path.* 5:545, 1929.

The following conclusions have been reached after studying oil immersion fields of tissues stained as described previously. The glomerular, capsular and tubular basement membranes are continuous and stain red with van Gieson, blue with Ohmori and dark blue with Mallory-Heidenhain azan-carmin. The capsule and tubules have an additional external, reticular, argyrophil covering. The glomerular basement membrane is thinner than that of the capsule and tubules. Pores have not been demonstrated, nor any elastic fiber content. The glomerular, capsular and tubular epithelium is continuous. The glomerular epithelial cells have abundant cytoplasm and large vesicular nuclei with one or more prominent nucleoli. These are only cells which lie outside the glomerular basement membrane. They form complete covering for the loops following closely both tips and crevices. They are arranged in a single layer and not in a syncytium. The glomerular endothelium lies inside the basement membrane and therefore cannot be confused with epithelium. The cytoplasm is very small in amount and the nuclei have a thick nuclear membrane enclosing much coarse chromatin. Endothelial cells are much less numerous than epithelial. There are cells, probably endothelial, which lie inside the glomerular basement membrane but are partially surrounded by it. Their nuclei seem to be identical with those of typical endothelium and they have very little cytoplasm. Their situation at the orifices between the loops makes examination very difficult. Further study to decide their nature is in progress. Connective tissue cells and reticulum fibrils pass in at the hilus accompanying the vas afferens until it subdivides near the center of the glomerulus.

AUTHOR'S SUMMARY.

THE CYTOLOGICAL CHANGES OCCURRING IN THE GLOMERULUS OF CLINICAL GLOMERULONEPHRITIS. LEONE MCGREGOR, *Am. J. Path.* 5:559, 1929.

From a microscopic study of glomeruli of sixty cases of acute and chronic glomerulonephritis the conclusions are as follows: The intracapillary cellular increase is chiefly endothelial and is explained by the numerous mitoses. The leukocytes are polymorphonuclear and are much less numerous than the endothelial cells. A small amount of fibrin and debris is found in most of the capillaries. The extracapillary changes consist of proliferation, degeneration and desquamation of glomerular and capsular epithelium. These are easily distinguished from intracapillary lesions because the glomerular basement membrane lies between. Crescent formation may be due to capsular epithelial proliferation or to a combination of capsular proliferation and glomerular epithelial desquamation. In a very early period, hyaline fibers appear between the cells and are soon continuous with the capsular basement membrane. Hyaline fibers also appear inside the glomerular capillaries. They stain blue with the Mallory-Heidenhain azan-carmin, or with Ohmori's rein blau and not at all with silver. When first formed, they lie between the proliferating endothelial cells and are usually attached to the basement membrane. They appear as fine sharp lines with knobs at intersections. They soon form a definite meshwork enclosing the intracapillary cells. This fibrous meshwork is believed to be an important and typical finding in glomerulonephritis. It is the initial stage of the hyalinization of the glomerulus. The process takes place in all the glomeruli but not always to the same degree. When the loops are only partially occluded, blood continues to circulate along one side and the

glomerulus has some function. When every loop is occluded, the circulation cannot continue. The fibers within the loop increase in number and caliber, many fuse, and the enclosed cells are atrophied by pressure. The glomerular loop arrives at a stage where it consists of a few flattened epithelial cells, a basement membrane and a lumen completely filled with a hyaline fibrous mass enclosing a few nuclei. Adjacent loops fuse, and the fibers contract. The glomerular epithelial atrophies and disappears. At the same time the fibers of the crescent have increased and contracted until they have eliminated most of the cells. The fibrous crescent now fuses with the fibrous glomerulus. The end-result is a sphere of fibrous connective tissue containing practically no nuclei. The origin and composition of the intracapillary hyaline fibers are undetermined and require further study. They do not seem to be fibrin or derivatives of it. They are thought to be a crystallization or precipitation of the intercellular exudate under the influence of the proliferating endothelial cells or perhaps a product of the glomerular basement membrane. Later they are indistinguishable from typical collagenous fibers. The foregoing processes are typical of clinical glomerulonephritis. The finding of a glomerular cellular increase (usually monocytes) following pneumonia and other infections is not to be confused with clinical nephritis. The nonclinical cases do not have the characteristic intracapillary fibrous meshwork.

AUTHOR'S SUMMARY.

LIPOID NEPHROSIS. E. T. BELL, *Am. J. Path.* 5:587, 1929.

A survey of the recent literature shows a tendency to use "lipoid nephrosis" in a broad way to include all cases of nephritis with edema, albuminuria, normal blood pressure and normal blood nitrogen. This clinical definition includes many cases that are anatomically acute or mild chronic glomerulonephritis. All the clinical phenomena of lipoid nephrosis, viz., albuminuria, edema, normal blood pressure, hypercholesterolemia, decrease of the plasma proteins with reversal of the albumin: globulin ratio and normal blood nitrogen, may occur in a less pronounced form in glomerulonephritis. There are many transition cases between lipoid nephrosis and glomerulonephritis, viz., those that fit the definition of lipoid nephrosis except for the presence of hypertension or moderate nitrogen retention. These are called the mixed type, or nephritis with a nephrotic Einschlag. From the clinical standpoint the two diseases cannot be sharply separated. A histologic study has been made of 10 cases of large, fatty kidneys, without tubular atrophy, that were clinically nephritis. Four of these are classed as pure lipoid nephrosis, 3 as nephritis with nephrotic Einschlag (mixed type) and 3 of uncertain type because of lack of clinical data. The glomeruli are not normal in any instance, but the lesions are not of uniform type. In pure lipoid nephrosis there is a varying increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane. In the mixed type (nephritis with nephrotic Einschlag) there is a marked thickening of the basement membrane. In one instance the capillaries were compressed by enlarged epithelial cells. In two instances there was a definite increase in the number and size of the glomerular endothelial cells, and a few areas in the glomeruli showed the changes characteristic of typical clinical glomerulonephritis, i. e., capillaries filled with endothelial cells and a network of hyaline fibers. Three large noncontracted kidneys were studied in which the data were insufficient to determine whether they should be classed as lipoid nephrosis. Two of these showed extreme thickening of the basement membrane. The third showed an enormous accumulation of fat in the tubules and glomeruli, large glomerular epithelial cells with hyaline and fatty degeneration, and leukocytes and hyaline fibers within the capillaries as in glomerulonephritis. Lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially obstructed so that they continue to function and tubular atrophy does not occur.

AUTHOR'S SUMMARY.

OBSTRUCTIVE CIRRHOSIS. H. E. MACMAHON and F. B. MALLORY, *Am. J. Path.* **5**:645, 1929.

This paper is based on the study of thirty cases of uncomplicated obstructive cirrhosis, ten in infants and twenty in adults averaging about 60 years of age. The common cause in infancy is a congenital malformation of the bile duct, whereas in the adult it results from tumors, concretions and inflammatory strictures. The gross and microscopic observations of obstructive cirrhosis are described, and in addition, reference is made to a few of its more important clinical features.

AUTHORS' SUMMARY.

HEMORRHAGES IN THE FUNDUS IN HYPERTENSION. FRITZ LANGE, *Arch. Ophth.* **2**:551, 1929.

With the recently established differential diagnosis of arteriosclerosis and hypertension, it becomes necessary to refer hemorrhages in the eye to their proper cause. Hemorrhages may occur anywhere in the retina. Of sixty patients examined, fifty-seven had high blood pressure (from 160 to 200 + mm. of hydrogen). In fifteen of these there was only hypertension without arteriosclerosis, and these showed characteristic changes in the arteries of the fundus, as to caliber and tortuosity. The other forty patients showed clinical signs of arteriosclerosis, the average age being higher than that of the pure hypertensions. No case of pure arteriosclerosis was found. In advanced cases of arteriosclerosis and hypertension the blood vessels of the fundus were changed in the same way, and as frequently as in pure hypertension; differentiation as to origin could not be made. The blood vessels show imbibitions of calcium and cholesterol in about 10 per cent of the arteriosclerotic cases, corresponding to the degree of clinical arteriosclerosis. For controls, patients with clinically pure arteriosclerosis and low blood pressure were examined, and each patient was found to be free of retinal hemorrhage. Only three of the sixty patients with retinal hemorrhage did not show hypertension, and in these the etiology was obscure; certainly it was not due to arteriosclerosis. Retinal hemorrhages in cases of diabetes and syphilis were found in conjunction with high blood pressure with but few exceptions. No cases of cerebral apoplexy without hypertension were found, unless the hypertension was masked by cardiac insufficiency. The same factors are responsible for retinal hemorrhage as for cerebral apoplexy, and both usually originate in the capillaries.

CHARLES WEISS.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM (TERATOID IN PAROTID REGION). ALFRED SCOTT WARTHIN, *J. Cancer Research* **13**:116, 1929.

The author reports, in great detail, two identical tumors which he found among "diagnostic material of several hundred thousand cases examined by him since 1895." He states that he could find no record in the literature of the existence of a similar blastoma. He designates the new growth as a "papilliferous cystadenoma lymphomatosum" which he regards as a very rare teratoid of the parotid gland region. It represents a heterotopia or dystopia of pharyngeal entoderm, resembling in structure most closely, the mucosa of the cartilaginous portion of the eustachian tube.

B. M. FRIED.

HISTOLOGICAL FINDINGS IN HEARTS WHICH HAVE BEEN EXPOSED TO RADIATION IN THE COURSE OF TREATMENT OF ADJACENT ORGANS. A. A. THIBAUDEAU and W. L. MATTICK, *J. Cancer Research* **13**:251, 1929.

The authors have selected for their study ten hearts secured at autopsy from patients in whom extensive radiation had been applied in the precordial region during the course of treatment of malignant condition of the heart. It appeared to them that radiation of the human heart as applied in the treatment of malignant neoplasm in its immediate vicinity may cause definite injury to the cardiac muscle.

The pathologic process varies from slight interstitial fibrosis to hyaline and fatty degeneration of the muscle fibers with necrosis.

B. M. FRIED.

CHOLESTEROSIS OF THE GALLBLADDER. C. F. W. ILLINGWORTH, *Brit. J. Surg.* **17**:203, 1929.

Of thirty-five cases of operation for disease of the gallbladder, twenty-one showed evidences of cholesterosis. The deposition of lipoids may be diffuse, patchy or polypoid as bright yellow areas located on the ridges of the mucosa which stand out distinctly against the surrounding red mucosa. The organ otherwise may appear grossly normal but more frequently it is thickened. The lipoids are situated in the mucous coat but occasionally in the fibromuscular layers, and the villi may be distended by foamy cells in the stroma. The bile was usually sterile, thick and tarry, but was clear and contained from 503 to 907 mg. per cent as compared to a normal determination of 329.

RICHARD A. LIFVENDAHL.

ENDOTHELIOMA OF THE NASOPHARYNX. A. J. GARDHAM, *Brit. J. Surg.* **17**:242, 1929.

This study covers nine cases. On the basis of clinical manifestations, the new growth is thought to have its origin in close relation to the eustachian tube, pharyngeal wall and fifth nerve. In the nasopharynx it appears as a firm, pink, small and sessile tumor in the region of the eustachian tube and tends to spread underneath the mucous membrane of the mouth, after involving the soft and hard palates. Further extension may occur to the base of the skull and ultimately may involve the outer surface of the cranium. In the course of this extension, the sensory and motor divisions of the fifth nerve, the sixth nerve—as the results of tumor invasion of the carotid canal or the sphenoidal sinus—and lastly the nerves of the palate may all be involved, resulting in symptoms referable to these structures. More rarely, however, any one of the cranial nerves may be affected by the neoplasm. Secondary deposits in the cervical lymph glands, on both sides of the neck, may occur before the primary growth is large enough to produce symptoms. The glands are hard, fixed and discrete and show no tendency to break down. Microscopically, the primary and secondary growths consist of large and irregular but mostly spheroidal cells, arranged in groups in a tubular fashion separated by connective tissue.

RICHARD A. LIFVENDAHL.

ANEURYSM OF THE SPLENIC ARTERY. W. ANDERSON and JOHN GRAY, *Brit. J. Surg.* **17**:267, 1929.

Degeneration and necrosis of the media of the splenic artery led to the formation of the saccular aneurysm and secondary extensive and fatal intraperitoneal hemorrhage. A review of fifty-eight collected instances did not show an outstanding causative factor, but in some septic embolism, arteriosclerosis and syphilis have been suggested.

RICHARD A. LIFVENDAHL.

PRIMARY JEJUNAL ULCER. J. M. BLACK, *Brit. J. Surg.* **17**:338, 1929.

A minute perforation surrounded by an acute inflammatory tract was found 2 feet distal to the commencement of the jejunum. Ulcers in this location are rare except following gastrojejunostomy. In this case there were no evidences of typhoid fever nor was there any history of trauma to the abdomen.

RICHARD A. LIFVENDAHL.

PATHOLOGIC GRANULATION OF FINELY GRANULATED LEUKOCYTES. H. MOMMSEN, *Klin. Wchnschr.* 8:2420, 1929.

With a Giemsa stain at pH 5.4, the normal finely granular leukocytes are without granules, while pathologically altered leukocytes (toxic) have granules. The granules are basophilic and not neutrophilic. The expression neutrophil leukocytes is therefore out of order, and should be replaced by finely granulated leukocytes. Pathologic granules in acute infectious diseases are not developed to a maximum at first, but only after several days, as in lobar pneumonia during the crisis.

AUTHOR'S SUMMARY (in part).

THROMBOSIS AND EMBOLISM IN POST WAR YEARS. T. K. KUHN, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 41:329, 1929.

In the postmortem examinations at Freiburg from 1921 to 1925, there was an increase in thrombosis from 11.3 to 24.5 per cent and an increase in fatal embolism from 1.3 to 4.9 per cent. The report concerns 665 cases of thrombosis and 105 of fatal embolism encountered in the years 1919 to 1927. After elaborate statistical evidence is offered, the author concludes: that thrombosis affects most people between the ages of 41 and 50 years and fatal emboli are seen mostly between the ages of 51 and 60 years; that thrombosis and embolism are more common in men than in women; that cardiac dilatation and hypertrophy precede thrombosis and embolism more frequently than any other disease; that thrombi and emboli are met with most frequently in the internal medical clinics, 31.6 per cent in 1927 as against 24.3 per cent in surgical clinics and 25 per cent in gynecologic clinics. The increase in the medical clinics is traceable directly or indirectly to the increase in intravenous therapy. Infections were associated with local thrombosis only in the first year after the war. Obesity is regarded as predisposing to embolism because 50 per cent of obese people died of emboli in the lungs whereas only 2.2 per cent of cachectic people were found dead from this cause.

GEORGE RUKSTINAT.

TOTAL ALYMPHOCYTOSIS. L. R. GROTE and B. FISCHER-WASELS, *München. med. Wchnschr.* 76:2040, 1929.

The authors report the case of a man, aged 39, with attacks simulating pancreatitis and indefinite symptoms of stenosis of the small bowel. After an illness of several months the increasing cachexia became associated with ascites and edema that were neither cardiac nor renal. The blood changed from normal to a complete absence of lymphocytes. Postmortem examination disclosed a total atrophy of the lymphatic system and of the spleen.

EDWIN F. HIRSCH.

A MALIGNANT THYOMA WITH METASTASIS TO THE CENTRAL NERVOUS SYSTEM IN A CHILD THREE AND A HALF YEARS OLD. F. DANISCH and E. NEDELMANN, *Virchows Arch. f. Path. Anat.* 268:492, 1928.

The author discusses a malignant lymphocytoma of the thymus with metastases to the central nervous system, cervical lymph nodes, heart and kidneys. An interesting aspect of the case is a marked pleocytosis of the spinal fluid due to the presence of numerous tumor cells.

K. HOSOI.

THE CHANGES IN LIVER WOUNDS AFTER PACKING WITH FREE AND ATTACHED OMENTAL GRAFTS. OSKAR LEWIN, *Virchows Arch. f. path. Anat.* 272:31, 1929.

In sixteen rabbits a liver wound was packed with a free omental graft, and in sixteen others with a pedunculated graft. The animals were killed and examined at various times thereafter. The changes in the liver tissue were the same in

both series. The "pluripotent Kupffer cells" play the most important rôle; they form histiocytes, macrophages, fibroblasts, new capillaries and myeloid blood cells. No regeneration of liver cells was seen, but some overgrowth of young bile ducts. The attached omental graft can be transformed into connective tissue within ten or twelve days; with the free graft it takes at least fourteen days, occasionally forty-one days. Large parts of the free grafts become necrotic. The amount of necrosis depends on the extent of necrosis in the edges of the wound in the liver.

ALFRED PLAUT.

ACQUIRED NODULAR SYPHILIS OF THE LUNG. FRANZ WINDHOLZ, *Virchows Arch. f. path. Anat.* **272:76**, 1929.

One of the few really convincing cases of syphilis of the lung is reported. The patient was 73 years old and died suddenly from extensive aortitis syphilitica and arteriosclerosis. There were no tuberculous lesions. The gummas were situated in the middle lobe of the right lung only. The diagnosis was made from the gross specimen. The collagenous and elastic fibers were well preserved in the necrosis and the granulation tissue. The Wassermann test and the Meinicke reaction were strongly positive.

ALFRED PLAUT.

THE CAUSE OF ACCIDENTAL INVOLUTION OF THYMUS GLAND. A. BABES, *Virchows Arch. f. path. Anat.* **272:93**, 1929.

The accidental involution of the thymus (Hammar) is no simple atrophy. The sclerosis and the storing of different fat substances and of iron speak against it. It is not due to general nutritional disturbances, but to inflammatory processes in the lung. The older the inflammatory disease of the lung, the more marked is the accidental involution of the thymus. Among forty-four cases, only one showed accidental involution without an inflammatory process in the lung. Babes believes that toxic substances originating in the inflamed lung cause the accidental involution of thymus.

ALFRED PLAUT.

THE IMPORTANCE OF THE RETICULIN FIBERS IN TUBERCULOSIS. P. A. ELIASCHEWITSCH, *Virchows Arch. f. path. Anat.* **272:151**, 1929.

The noncellular tissue constituents often are neglected. Even the youngest and smallest tubercles, which do not yet contain giant cells, have a reticulum. There are a few fine fibers in the center, and there is a peripheral fibrillary layer. Small resorption tubercles in the surroundings of cheesy areas are best suited for the study. The reticulum is present before any healing tendencies, any fibrous change or any attempts at separation from the surroundings can be noted. The reticulin fibers ("Gitterfasern") are highly resistant to caseation. The fibrous change in a tubercle often is due to thickening of the existing reticulum rather than to multiplication of fibroblasts. With the growth of the tubercle, the fibers hypertrophy and finally become collagenous. The concentric, often entirely enclosed, fibrillary system of the tubercle seems to be important for the fixation of bacilli and toxins. In fact, bacilli can be found directly on the fibrils or the lamellae between them. The reticulum seems to have some adsorptive immunologic action. One must not think of the reticulin fibers as a merely mechanical device. The physicochemical condition of the reticulum may well play a rôle in the localization of the tuberculous process.

ALFRED PLAUT.

TISSUE CULTURE OF HUMAN CHORIONIC EPITHELIUM. E. A. H. FRIEDHEIM, *Virchows Arch. f. path. Anat.* **272:217**, 1929.

The question whether the large cells that are found deep in the muscle of the puerperal uterus are chorionic cells that have migrated or are formed from the

mesenchyma cannot be answered by usual histologic methods. Therefore tissue cultures were made from chorionic villi of a 5 weeks old tubal gestation. The result favors the theory that these cells are migrating Langhans cells because the cells grow very well and in pure epithelial culture from the beginning. They liquefy the medium moderately and are motile. The syncytial cells, on the other hand, do not liquefy the medium and they do not grow at all. Isolated fragments of syncytial protoplasm, however, containing no nuclei, may show motility for several hours.

ALFRED PLAUT.

COMPLICATED MALFORMATION OF UROGENITAL ORGANS. F. A. LENTZE, *Virchows Arch. f. path. Anat.* **272**:279, 1929.

Ball-shaped dilatation of the ureter above the bladder is reported, with cystic horse-shoe kidney, double ureter on the other side, diverticulum of the bladder, dilatation of the urethra, malformation of the sphincter, marked hypoplasia of the prostate, absence of both seminal vesicles and of one vas deferens, large utriculus, scoliosis, spina bifida and clubfeet.

ALFRED PLAUT.

THE OS SACRUM. E. BRACK, *Virchows Arch. f. path.* **272**:295, 1929.

There is reported the absence of a sacrum in a new-born infant with extremely hypoplastic lower extremities; fracture of the os sacrum causing periproctal hemorrhage; ruptured sacral meningocele causing death through loss of cerebrospinal fluid in a 61 year old woman; smaller similar unruptured cyst in a man 80 years old.

The cartilaginous nodules may occur in the disks of the os sacrum.

ALFRED PLAUT.

GAUCHER-LIKE CHANGES IN THE SPLEEN OF TAR-PAINTED RABBITS. A. BABÉS, *Virchows Arch. f. path. Anat.* **272**:411, 1929.

Three of five rabbits which died between the tenth and twentieth day after the onset of tar painting had Gaucher-like changes in the spleen. The spleen is large, chocolate brown, with few and small follicles. The slides can hardly be recognized as spleen since most of the tissue is supplanted by strands and alveoli of large clear Gaucher-like cells, mostly from 18 to 30 microns in diameter, with large clear central nucleus and one or two nucleoli. The protoplasm contains no lipid substance; little iron is stored. Most of the large cells are situated within a sinus, few within a pulp cord. In this respect the condition differs from Gaucher's disease of spleen. L. Pick has seen the slides and agrees that the cells are similar to those found in Gaucher's disease. It is important to have a Gaucher-like condition which is caused by a well defined substance.

ALFRED PLAUT.

AMYLOID DEPOSITS IN SEMINAL VESICLES. ELMAR ERLACH, *Virchows Arch. f. path. Anat.* **272**:418, 1929.

A description of three cases is given. The condition is rare. Since its gross appearance is not unlike that of tuberculosis with caseation, some cases may be overlooked at autopsy.

ALFRED PLAUT.

PERIARTERITIS NODOSA. JOSEF BALÓ and E. NACTNEBEL, *Virchows Arch. f. path. Anat.* **272**:478, 1929.

Nine cases were observed in Budapest within three years. The disease seems to be more frequent in Germany and Austria than in other countries. The authors think that the disease is infectious. Many cases have been observed

among stags in a park in the south of Germany. All nine cases were diagnosed from the gross aspect at autopsy. In five patients who had no nervous symptoms, severe lesions were found in the blood vessels of the nerves, but no marked degeneration of the nerve substance. Thus the nerve degeneration cannot be caused by the vascular lesion alone. Animal inoculation failed.

ALFRED PLAUT.

SPLENOMYCOSIS AND MYCOTIC SPLENOMEGALY. A. A. ABRIKOSSOFF, *Virchows Arch. f. path. Anat.* **272**:593, 1929.

Abrikossoff retracts his statement of 1928. He now believes that the formations in the spleen which have been described by many authors, especially the French, have nothing to do with mycelium. He believes that they originate (as German authors and some of the French always believed) from incrustation of connective tissue fibers, fibrin or erythrocytes. The round bodies that have been described as fructification organs of the fungus are too variable in size, and similar structures can result from iron salt solutions in vitro. The fact that *Aspergillus* may be grown from such spleens does not prove that the incrustations in question are mycelium. Thus no mycotic splenomegaly has been proved and the existence of such a disease is not probable.

ALFRED PLAUT.

MARKED FUNNEL CHEST. FRANZ STADTMÜLLER, *Virchows Arch. f. path. Anat.* **272**:641, 1929.

The author gives an exact description of a funnel-breast. In spite of the malformation, the heart was nearly in normal position. There was a large vertical space-furrow in the right lobe of the liver without a fold of diaphragm in it. This confirms Westenhöfer's conception that these folds are due to lateral compression of the liver.

ALFRED PLAUT.

ECHINOCOCCUS DISEASE OF THE PELVIC BONES. FRANZ ALTMANN, *Virchows Arch. f. path. Anat.* **272**:662, 1929.

From 1 to 2 per cent of *Echinococcus* infections are located in the bones. Next to the spine, the pelvis is the preferred site. In the pelvis the disease generally starts in the region of the acetabulum.

A woman, aged 46, had had symptoms in the right hip for twenty-six years. She fell down several times. Eighteen years before the present observations she was operated on for *Echinococcus* in the abdomen. She died shortly after two operations which were necessitated by excessive swelling of the hip region and thigh. The pelvis, both thighs and the corresponding muscle were removed from the body at autopsy. Large cysts were found in the muscles of the thigh and the pelvis. Most of the upper end of the femur was destroyed. There was severe destruction of all pelvic bones on the right side. Bone sequestrs contained numerous small vesicles. The bone was destroyed by lacunar arrosion with formation of sequestrs. The bone marrow contained granulation tissue with giant cells; there were no thick connective tissue capsules around the parasites. Many small, partly calcified osteoid layers were present. Some isolated, lime-free spots (Pommer's method) in otherwise normal spongiosa were suggestive of halisteresis.

Similar lesions were found in the museum specimen from an autopsy by Rokitsky in 1834. The tissue could be cut and stained well.

Fifty-three cases of primary *Echinococcus* disease of the pelvis are enumerated in a classified list.

ALFRED PLAUT.

THE REGRESSION OF EXPERIMENTAL LIPIDOSIS IN THE RABBIT EYE. A. A. KOLEN, *Virchows Arch. f. path. Anat.* **272**:679, 1929.

Experimental lipoidosis in the rabbit eye is similar to gerontoxon in man. There is a difference in that the lipoid material in gerontoxon is mostly situated

in connective tissue structures, and not in cells. After cessation of the cholesterol feeding, very strong experimental lipoidosis may remain up to three years. During the regression, the crescent-shaped lipoidosis occasionally shifts toward the center of the cornea. The periphery partly becomes clear. During regression, the infiltrated parts of the cornea become mottled and glistening like mother-of-pearl. Similar regressive changes are noted occasionally in gerontoxon in man. In the rabbit the superficial vascular layer of connective tissue forms during regression of very marked lipoidosis.

ALFRED PLAUT.

SOCALLED EXPERIMENTAL CHOLESTERIN STEATOSIS OF RABBIT AND OTHER ANIMALS. S. S. CHALATOW, *Virchows Arch. f. path. Anat.* **272**:691, 1929.

Cholesterin steatosis is complex. In any experiment one should take account of qualitative and quantitative variations carefully. The irritation that anisotropic lipoids exert on cells is due to their physical nature; it is not chemical. Tumorous xanthomas are formed by the same process. Chalатов denies the existence of a physiologic reticulo-endothelial system. The fact that the Kupffer cells, for instance, retain corpuscles and micro-organisms has nothing to do with phagocytosis. Anisotropic fatty change is always preceded by infiltration with isotropic fat. The cholesterin steatosis has different localization in different animals (intima of the aorta in man). Sclerosis and xanthomatosis exclude each other, as one can see in syphilitic aortitis. While interpreting the results of feeding experiments on goats, the author again stresses the complexity of the problem and hints that not all the conclusions drawn in the literature are valid.

ALFRED PLAUT.

THE FROG'S TONGUE AFTER THE INJECTION OF INDIA INK INTO THE BLOODSTREAM. W. SCHOPPER, *Virchows Arch. f. path. Anat.* **272**:709, 1929.

The storage of india ink is a purely physical process. The cells of the walls of peripheral blood vessels also can store the india ink, as can be seen on the tongue of the living frog. They do not store as intensely as do the reticulum cells of the spleen and the Kupffer cells in the liver. In the experiments, the tongue was gently stretched over a ring of cork; the animal was anesthetized by the injection of urethane into the dorsal lymph sac. Lymphocytes and large monocytes stored the india ink also; neutrophil and eosinophil leukocytes remained nearly free. The india ink was located on granulations in the cells of the vessel wall. Most of the monocytes probably originated from the lining cells of liver capillaries. In the course of weeks, the india ink was brought into the perivascular tissue by means of the adventitial cells.

ALFRED PLAUT.

THE REACTION OF THE ENDOTHELIUM OF THE RABBIT CAROTID ARTERY AFTER DOUBLE LIGATION. B. F. MALYSCHEW, *Virchows Arch. f. path. Anat.* **272**:727, 1929.

In the rabbit carotid, the endothelium rests directly on the inner elastic layer. There is no connective tissue between both. The vasa vasorum reach only into the outer muscular layers. Thus one can be sure that all cells found within the lumen of the ligated vessel originate from endothelium.

The experiments were done on forty-nine rabbits. The ligatures were made from 0.25 to 1 cm. apart; sometimes the peripheral ligature was made first, and sometimes the central. The observations were made after different periods of time—from six hours to one year. In another group of animals the artery was cut between two double ligatures. The same was done in a third group, and the artery was then put into the peritoneal cavity of the rabbit. In some animals trypan blue was injected into the ear vein.

Practically no thrombosis took place. There was intensive overgrowth of the endothelial cells, not only parallel to the vessel wall, but also at right angles, with the formation of so-called cavernoma. The endothelial cells became partly

separated from the vessel wall and grew like a tissue culture in the plasma of the blood. The red blood cells disappeared after four or five weeks only, when granulation tissue began to grow into the lumen. The leukocytes disappeared earlier, the lymphocytes being more resistant than the granular forms. There was no sign of multiplication of blood cells or of transformation into other forms. Between the first and the fourth week, complete hematopoiesis was observed in the doubly ligated part of the artery. The whole process was intravascular. The endothelial cells formed a connective tissue layer inside the internal elastic lamella, and in later stages this layer was transformed into a musculo-elastic layer. It is probable that these elastic fibers and muscle cells developed from the fibroblasts, which in turn originated from the endothelium. In the sections of artery which were put into the abdominal cavity, the tissue reactions were the same.

ALFRED PLAUT.

EXPERIMENTAL INVESTIGATIONS ON SPLEEN CHANGES IN PERITONITIS. P. GOHRBANDT, Virchows Arch. f. path. Anat. **272**:763, 1929.

It was the author's purpose to study changes in the spleen in peritonitis which have never been described in full in the literature. Dogs were laparotomized, and a small piece from the spleen was excised. Then peritonitis was caused by opening the stomach, the colon or the gallbladder, or by bringing bacteria into the peritoneal cavity. Occasionally another biopsy was taken later. The dogs were killed by the injection of chloroform into the heart.

The dog spleen contains many more muscle fibers than that of the human being. There is a distinct perifollicular zone around the malpighian bodies; its cells are similar to those of the germ centers. Eosinophil cells are few. Polymorphonuclear leukocytes are always found, especially in the perifollicular zone under the capsule and along the trabeculae. There are plasma cells in the spleens of most dogs.

Swelling of the spleen was not found in any of the experiments. On the other hand, a bitch that had general septicemia after necrotic metritis showed swelling of the spleen at the time of death. The softness and swelling of the spleen as found in autopsies of human beings after septic diseases probably are mostly postmortem. Microscopic changes were present in every spleen examined. In order to appreciate these changes, it is necessary to have the comparison with the biopsy which was taken before the onset of the peritonitis. The malpighian bodies generally are not swollen and the germ centers not enlarged. Necroses are found frequently in the centers, occasionally in the perifollicular zone also. Very little necrosis was found in the pulpa. These lesions are similar to the ones described in infectious diseases and poisonings. The lymphoblasts are most damaged. The necrotic lesions were found more frequently after biliary peritonitis; they are probably toxic in origin.

The amount of histochemically demonstrable fat was increased, but the fat in the capillary sheaths shown by the biopsy was absent in the autopsy material. The necrotic spots were surrounded by much fat. The iron pigment was generally increased. The distribution of leukocytes was studied with the oxydase reaction. They increase in the first ten hours of peritonitis; they then decrease and appear mostly in the perifollicular zone. The true and the lymphoblastic plasma cells were generally increased in number. Myeloid metaplasia was found twice. The productive changes were mostly localized around the necrotic spots. There were some giant cells.

Even the most virulent cultures of *Bacterium coli* did not cause fatal peritonitis, not even when gauze was left in the peritoneal cavity and opiates were used to lower the intestinal activity. *Staphylococcus* cultures were not very efficient either, while streptococci proved more virulent.

ALFRED PLAUT.

TRAUMATIC ANEURYSM. HAROLD BORCHARDT, *Virchows Arch. f. path. Anat.* **273**:163, 1929.

A man, aged 19 years, fell while walking. He hit a stone with his left side and broke a rib. For the next thirty years he continuously had pain in the left side. Forty-five years later, while he was in bed in a hospital (with jaundice), he suddenly died with the symptoms of internal hemorrhage. A circumscribed shadow in the left side of the chest had been seen in the x-ray picture. Autopsy revealed an aneurysm of the muscular branch of the left fourth intercostal artery. It had eroded the bone of the rib and of the vertebra considerably. Thus the pain which the man had had for thirty years is explained by the pressure of the nerve root.

ALFRED PLAUT.

THE TAR AND CHOCOLATE CYSTS OF THE OVARY. F. ISBRUCH, *Ztschr. f. Geburtsh. u. Gynäk.* **94**:710, 1929.

In a woman with complete obstruction of the cervix, tar cysts were found in both ovaries. Dysmenorrhea was present for many years, but no hemorrhage. The case is not considered as a proof of Sampson's implantation theory of the origin of endometrial cysts due to retrograde menstruation, as there is still definite evidence lacking that endometrial tissue desquamated during menstruation is able to become implanted and to grow successfully. This question may be decided through tissue cultures of endometrial tissue.

W. C. HUEPER.

DIFFUSE MELANOSARCOMATOSIS OF THE SOFT MENINGES. J. KRAFT, *Ztschr. f. Krebsforsch.* **29**:74, 1929.

A case is reported of primary diffuse melanotic tumor of the soft meninges of the brain and cord. Although its microscopic appearance was that of a sarcoma, there was nowhere evidence of metastasis outside of the leptomeninges; but here the tumor appeared to be capable of indefinite extension, even into the clefts and sulci of the brain and cord surfaces. The writer cites a small number of similar cases previously reported.

H. E. EGGERS.

PECULIAR PROPERTIES OF CANCEROUS PLEURAL EXUDATE. H. AULER and P. MEYER, *Ztschr. f. Krebsforsch.* **30**:286, 1929.

In the pleural exudate formed as a result of metastasis of a cancer of the breast, the writers have found a high content of complement, the more remarkable because cancerous serum ordinarily shows a great reduction in this component. Unlike the normal complement of guinea-pig serum, this withstood from twelve to fourteen days' storage in the icebox. Another peculiarity lay in the fact that after separation of the rapidly developing spontaneous clot, there was further clotting on the addition of alcoholic antigens diluted as for the Wassermann test.

H. E. EGGERS.

THE EXPLANTATION OF ENDOMETRIUM. P. CAFFIER, *Zentralbl. f. Gynäk.* **52**:63, 1928.

A veil-like membrane always developed around the explanted endometrium, regardless of during which phase of the cycle the endometrial tissue was explanted. Decidua of the first months showed the same product. A separation of the cells in the cellular sprouts around the explanted tissue into cells of different origin was not possible. Endometrial tissue desquamated during menstruation could not be successfully cultured. Definite conclusions from these results could not be drawn on Sampson's theory of endometriomas.

W. C. HUEPER.

INFILTRATIONS IN SMALL INTESTINE WITH PLASMA CELLS. U. QUENSEL, Finska läk.-sällsk. handl. **71**:661, 1929.

In a man, aged 44, with a history of long-continued gastric disturbance and treatment for duodenal ulcer, there occurred suddenly great exhaustion with bloody feces and death in a week. Necropsy revealed numerous firm, round and oval foci of various sizes. Most of the mucous membrane was intact. Microscopic examination showed a diffuse infiltration of the intestinal wall with round cells, chiefly plasma cells. In and among these cells were peculiar, sharply defined foreign corpuscles of irregular form and size. It is suggested that the process may perhaps be regarded as a new mycotic disorder of the intestine.

Pathologic Chemistry and Physics

SOME PHYSIOLOGICAL ASPECTS OF COPPER IN THE ORGANISM. F. B. FLINN and J. M. INOUE, J. Biol. Chem. **84**:101, 1929.

Ingested copper is eliminated, almost entirely, in the feces. A part becomes intermediately absorbed into the body but is rapidly returned to the intestines in the biliary excretions. The distribution of copper in the tissues of the rat, and in the livers of the different animal species; the affinity of the metal for protein, and especially for mucin; and the possibility that copper may favor growth and hemoglobin production are discussed.

ARTHUR LOCKE.

THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN ECLAMPSIA. H. J. STANDER, N. J. EASTMAN, E. P. H. HARRISON, JR., and J. F. CADDEN, J. Biol. Chem. **85**:233, 1929.

Severe eclampsia is associated with a true acidosis, due to an uncompensated alkali deficit. The organic acid content of the blood is increased, and the p_H is decidedly lowered. There is no increase in organic acid content or any abnormal reduction in the p_H of the blood during normal pregnancy.

ARTHUR LOCKE.

THE NATURE OF THE EFFECT OF A HIGH-FREQUENCY ELECTRIC FIELD UPON PARAMÆCIUM. H. KÄHLER, H. W. CHALKLEY and CARL VOEGTLIN, Pub. Health Rep. **44**:339, 1929.

It is shown that the only demonstrable effect of the exposure of *Paramæcium caudatum* to a high-frequency electrostatic or electromagnetic field is that primarily caused by a temperature increase in the organism. This conclusion is in agreement with deductions made from physical considerations of the effect of the high-frequency field on nonliving systems. Valid conclusions can be obtained only if due consideration is given to the control of certain complicating factors, such as the so-called skin effect and the energy output of the generating circuit.

AUTHORS' SUMMARY.

CRITICAL TEMPERATURE OF FREEZING LIVING MUSCLE. J. MORAN, Proc. Roy. Soc. s. B. **105**:177, 1929.

In the removal of water from living amphibian muscle, either by freezing or drying, three zones may be distinguished: (1) up to 40 per cent, over which the original state of muscle is completely recovered by restoring water; (2) between 40 and 78 per cent, in which the physiologic activity of the muscle progressively diminishes but its physicochemical properties are unaltered; (3) beyond 78 per cent, in which the muscle immediately dies. The critical water removal of 78 per cent corresponds to the freezing of the muscle to equilibrium at about -2°C .

Muscles frozen to equilibrium below -2°C . undergo marked changes on thawing, such as (1) shortening up to 80 per cent of the length of the muscle, (2) expression of a strongly acid fluid, (3) total loss of irritability and (4) complete loss of osmotic properties. Of these the shortening alone can be prevented; it does not occur when the frozen muscle is very slowly thawed. Muscles supercooled below -2°C . (e. g., for two days at -4°C .) do not undergo irreversible change. They appear to be normal when restored to room temperature.

AUTHOR'S SUMMARY.

THE FORMATION OF LACTIC ACID IN THE MUSCLES IN THE FROZEN STATE. E. C. SMITH, *Proc. Roy. Soc. s. B.* **105**:198, 1929.

A normal muscle with an adequate supply of oxygen is in a steady state in which the rate of production of lactic acid and of its removal are so balanced that the percentage of acid at any moment remains at a very low constant level. Freezing, that is, drying, upsets this balance by making the rate of production exceed that of removal. The upset in the balance is due to, or is accompanied by, injury to the mechanism, but in a storage period of twenty-four hours at temperatures between the freezing point and -1.6°C ., the mechanism of removal is not destroyed so that on thawing the accumulated acid is removed completely. Below -1.6°C . the mechanism of removal of acid is destroyed while that of production persists. Is it fair to ask whether the mechanism of removal is not the "living" part?

AUTHOR'S SUMMARY.

THE CHEMICAL BASIS AND THE CLINICAL SIGNIFICANCE OF PROTEIN DIFFERENTIATION IN THE SERUM. ANTON FISCHER, *Klin. Wchnschr.* **8**:2328, 1929.

Tryptophan estimations, which are an indirect chemical method for determining the albumin-globulin ratio, have a greater significance as a clinical indicator for active inflammatory diseases than the sedimentation reaction, especially in rheumatic diseases.

The diminution of the cystine content of pathologic serums is further evidence that under conditions that result in a globulin increase of the serum there are profound chemical changes of the serum proteins.

According to the results obtained, the globulin fraction is a mixture of four, and the albumin of three, chemically different proteins.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

SPONTANEOUS BACILLURIA AND PYELITIS IN THE RABBIT. HENRY F. HELMHOLZ, *Am. J. Dis. Child.* **38**:968, 1929.

Bacilluria is an infrequent observation in the catheterization of rabbits as a routine and is usually due to a gram-negative bacillus. The bacilluria is usually limited to the bladder but occasionally involves also the pelvis and the kidney. Exceptionally, cystitis, pyelitis and pyelonephritis are found in the rabbit. The frequency of bacilluria limited to the bladder and the relative infrequency of infection of the upper urinary passages make it probable that the exceptional bacilluria of the upper urinary tract and pyelonephritis are the result of an ascending infection from the bladder. So far as this study of spontaneous urinary infection is applicable to conditions in human beings, the conclusion seems warranted that infections of the urinary tract in infants take place by the ascending route.

AUTHOR'S SUMMARY.

MULTIPLE DISSEMINATED LUPUS VULGARIS [EMBOLIC TUBERCULOSIS]. VAUGHN C. GARNER, Am. J. Dis. Child. **38**:1028, 1929.

The disease is due to tubercle bacilli which reach the skin as emboli from an underlying focus which is usually glandular. In the majority of cases an exanthem, most often measles, acts as the exciting cause of this tuberculous dissemination. Clinically, the skin lesions are papular or verrucose, widespread and indurated. The association of tuberculous bone lesions is not infrequent. The ultimate prognosis must be guarded; an eventual mortality of 20 per cent is to be expected. The pediatrician's interest in this supposedly rare entity is solicited; a knowledge of its clinical features should lead to more frequent recognition.

AUTHOR'S SUMMARY.

UNDULANT FEVER PRESENTING THE CLINICAL SYNDROME OF INTERMITTENT HYDRARTHROSIS. B. M. BAKER, JR., Arch. Int. Med. **44**:128, 1929.

A case of infection by *Bacillus abortus* arising in Virginia is reported. In addition to many of the features of undulant fever, the patient presented a periodic swelling of the knee joints, diagnosed intermittent hydrarthrosis. Organisms of the *Brucella melitensis* group were isolated repeatedly from the blood stream and from fluid from the knee joints. Specific agglutinins appeared in the blood after the administration of an autogenous vaccine. Definite disappearance of the signs and symptoms of the infectious disease followed the administration of *Brucella melitensis* vaccine and serum from a patient who had recovered from undulant fever. There was amelioration of the subjective joint disturbances and a temporary alteration in the hydrarthrosis following this treatment. It is concluded that in this case the intermittent hydrarthrosis was part of the general picture of infection from *Brucella melitensis*, and it is suggested that infection by a member of this group of organisms might prove to be the cause of the clinical syndrome, intermittent hydrarthrosis, in other patients.

AUTHOR'S SUMMARY.

MENINGO-ENCEPHALITIS DUE TO TORULA. W. J. STONE and B. F. STURDIVANT, Arch. Int. Med. **44**:560, 1929.

There was a focus of torulosis in the apex of the right lung which is regarded as primary. The lesions of torulosis have numerous giant cells containing torulae but are free from polymorphonuclear leukocytes. All cases so far reported of *Torula meningitis* have ended in death.

THE RELATIONSHIP OF THE FLAVOBACTERIUM OPHTHALMIAE TO PERIODIC OPHTHALMIA IN HORSES. ALAN C. WOODS and E. L. BURKY, Arch. Ophth. **2**:456, 1929.

Investigations were made with a view to determining whether the asserted etiologic relationship of Rosenow's *Flavobacterium ophthalmiae* to moon blindness of horses could be confirmed. The organism as supplied by Rosenow was proteolytic and nonacid-forming. Cultures were taken, according to Rosenow's technic, from horses in which the disease was active as well as from normal horses. Fodder and farm water were also cultured. Cultures from normal and those from affected animals kept under the same conditions were both positive in about the same percentage; cultures from horses on farms on which the disease did not exist were positive a little less frequently than cultures from affected animals. On farms on which the disease was present, the organism was found in one of three cultures made of the fodder. No cultures of fodder from unaffected farms were made. No conclusions could be drawn from the results of cultures from the water supply. Four animals with acute exacerbation were killed, the eyes removed and cultures made under various conditions and on various mediums. These were all negative. The same results were obtained with the eyes of horses

in which the disease was quiescent. Agglutination tests showed apparently no difference in the agglutinative powers of serums from normal and affected horses toward this organism and no difference in the agglutinative power of an immune serum toward strains isolated from affected and normal horses. Intravenous injection of this organism did not affect the eyes. Intra-ocular injection produced moderate secondary uveitis, not comparable with periodic ophthalmia from either the clinical or the pathologic standpoint. Similar tests were made with broth cultures and filtrates of *B. prodigiosus* and *B. pyocyaneus* on rabbits, as well as with *Flavobacterium ophthalmiae*, and the results were found exactly similar in all three, a reaction that seems to be due to a product of protein degeneration. The authors conclude that *Flavobacterium ophthalmiae* is not the etiologic agent of periodic ophthalmia.

CHARLES WEISS.

FILTRABLE AGENT IN PERIODIC OPHTHALMIA OF HORSES. ALAN C. WOODS and A. M. CHESNEY, Thirteenth Concilium Ophthalmologicum, Amsterdam, Dan Haag, September, 1929.

A filtrable agent has been isolated from the eyes of horses affected with periodic ophthalmia. This agent has been passed through successive generations of rabbits by intra-ocular injections, producing the picture of an exudative retinitis. After passage through rabbits, it has again been transmitted to horses by intra-ocular injections, producing the pathologic picture found in the spontaneous disease.

THE EFFECT UPON HAEMOLYTIC STREPTOCOCCI OF CULTIVATING THEM IN IMMUNE AND NORMAL SERUM. ELEANOR A. BLISS and HAROLD L. AMOSS, Bull. Johns Hopkins Hosp. 45:361, 1929.

Two strains of erysipelas streptococci were found, after cultivation in homologous immune serum, to have deteriorated in toxigenicity and in pathogenicity for rabbits, while the same strains cultivated in normal horse serum maintained their original potency. In broth, the normal serum strain as well as the original culture produced a coarse precipitate, while the immune serum strain grew diffusely. The other biologic properties, such as fermentation reactions, hemolytic power and colony formation, of the two strains remained unchanged. Two kinds of colonies, rough and smooth, were observed on plates from the immune serum series and the original cultures. There was no difference in the pathogenicity for rabbits of a rough and smooth colony strain from a given culture. Those from the normal serum were equally virulent, while those from the immune serum were equally attenuated.

AUTHORS' SUMMARY.

UNDULANT FEVER. W. M. SIMPSON and E. FRAIZER, J. A. M. A. 93:1958, 1929.

Sixty-three cases of undulant fever have been discovered in and about Dayton, Ohio, during the past year. The rapidly increasing number of reported cases in the United States indicates the seriousness of this disease as a public health problem. Contrary to previously expressed beliefs as to the difficulties encountered in making a clinical diagnosis of undulant fever, the clinical picture of the disease was sufficiently characteristic to enable several physicians to make an initial diagnosis of undulant fever in more than one third of our cases. There appears to be no etiologic factor other than the ingestion of raw milk and unpasteurized dairy products in the cases studied. No cases of direct porcine or caprine origin were encountered. *Brucella abortus* was recovered from the blood of five patients suffering acutely from the disease. The organisms were found to be serologically identical with the strains recovered from the milk of five cows supplying raw milk to these patients. The blood was found to agglutinate *B. abortus* and *B. melitensis* in high titers. All were raw milk consumers. In three human cases of suppurating seminal vesiculitis, prostatitis, epididymitis and orchitis, antiabortus agglutinins were present in high titer. The organism was recovered from a

draining sinus tract of the scrotum in one case. The intradermal test utilizing a suspension of killed *abortus* organisms seems to hold considerable promise as an adjunct to the agglutination test.

AUTHORS' SUMMARY.

THE SPECIFICITY OF SCARLATINAL HEMOLYTIC STREPTOCOCCI. GEORGE MORIWAKI, J. Bact. 18:139, 1929.

In no respect has an absolute specificity of scarlatinal hemolytic streptococci been established. Every biologic as well as antigenic property tested seems common to a certain extent among strains of hemolytic streptococci from various sources. Especially, it is worth while to note that the rash-developing property is not limited to scarlatinal strains. These facts superficially seem to show that hemolytic streptococci primarily have no relation to the etiology of scarlatina, as was believed by Jochmann and others. But on the other hand, the fact that filtrates of broth culture of scarlatinal hemolytic streptococci contain scarlatinal antigen is well established, as shown by their rash-developing property and Schultz-Charlton's blanching phenomenon. Hemolytic streptococci from other sources also produce such an antigen. Therefore, the presence of a special filtrable virus of scarlatina may be doubted simply because the presence of such special virus, if any, together with streptococci from other sources than scarlatina is difficult to understand. The rash-developing power and the property of evoking Schultz-Charlton's phenomenon are properties of scarlatinal hemolytic streptococci, but these properties are common to hemolytic streptococci from other sources though in quantitatively less degree. Is there an unknown virus which makes hemolytic streptococci active? This is another problem. Finally the question arises as to the nature of scarlatinal symptoms: Are they toxic or allergic in relation to the product of the scarlatinal strain? The question has to be decided by further experimental studies.

AUTHOR'S SUMMARY.

BACTERIOLOGY OF THE BLOOD AND JOINTS IN RHEUMATIC FEVER. RUSSELL L. CECIL, EDITH E. NICHOLLS and WENDELL J. STAINSBY, J. Exper. Med. 50:617, 1929.

During the spring of 1928, twenty-nine patients with acute rheumatic fever were subjected to blood cultures, of whom nine, or 31 per cent, yielded a streptococcus. During the spring of 1929, thirty-one patients with acute rheumatic fever were studied by blood cultures, of whom twenty-six, or 83.9 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the thirty-five strains of streptococci recovered from blood cultures, thirty-three have been classified as alpha streptococci (*Streptococcus viridans*); one as a beta streptococcus (*Streptococcus hemolyticus*); and one a gamma streptococcus (*Streptococcus anhemolyticus*). Some of the viridans strains produced very little green on blood mediums. Agglutination and absorption tests indicate that the strains of *Streptococcus viridans* recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biologic groups. In seven patients with rheumatic fever who were subjected to cultures from affected joints, five, or 71.4 per cent, yielded *Streptococcus viridans*. In three patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These observations corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection, usually of the alpha or viridans type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent on localization of bacteria in the joint, with subsequent infection.

AUTHORS' SUMMARY.

DEVELOPMENT IN TISSUE CULTURES OF THE INTRACELLULAR CHANGES CHARACTERISTIC OF VACCINAL AND HERPETIC INFECTIONS. T. M. RIVERS, E. HAAGEN and R. S. MUCKENFUSS, J. Exper. Med. **50**:665, 1929.

Characteristic vaccinal and herpetic lesions, including Guarnieri's bodies and acidophilic nuclear inclusions, respectively, regularly occur in rabbit corneas infected and cultivated in vitro according to the method here described.

AUTHORS' SUMMARY.

STAPHYLOCOCCAL INFECTION AND REINFECTION. P. N. PANTON and F. C. O. VALENTINE, Brit. J. Exper. Path. **10**:257, 1929.

Experiments are reported which showed that repeated reinfection with *Staphylococcus aureus* produced a partial tissue immunity as demonstrated by the smaller skin reaction in response to a normal infective dose. In addition there was a partial or complete general immunity, evidenced by the appearance of agglutinins and increased resistance to a lethal dose. However, a very small dose which caused no symptoms in the control animals produced a definite reaction in those which were reinfected. It is believed that this increased sensitivity may result in further lesions in spite of the antibacterial substances produced.

J. N. PATTERSON.

TYPHUS FEVER RESERVOIR IN MAN. S. RAMSINE, Arch. Inst. Pasteur de Tunis **18**:247, 1929.

The author investigated a small isolated group of persons near Belgrade to whom typhus had been brought from a region where typhus was endemic. Positive Weil-Felix agglutination titers and the existence of the infective virus as tested by inoculation of guinea-pigs were clearly demonstrated in the blood of persons without clinical symptoms. In a succeeding paper, Charles Nicolle points out the importance of the proof of the existence of a latent reservoir for the virus in regions where the disease persists.

M. S. MARSHALL.

EVOLUTION OF SPIROCHETES IN THE TICK. PIERRE HATT, Arch. Inst. Pasteur de Tunis **18**:258, 1929.

The evolution of several species of spirochetes of recurrent fever in the bodies of *Ornithodoros moubata* and other ticks was studied. A fragmentation of the organisms was observed, resulting in a small stage, possibly a point of departure for a new cycle.

M. S. MARSHALL.

ATYPICAL PLASMODIA IN GRAVE CASES OF MALARIA. GEORGES VILLAIN, Arch. Inst. Pasteur de Tunis **18**:352, 1929.

Sketches of atypical forms of *Plasmodium falciparum* in the schizont stage are appended. The author concludes as follows: "From the medical point of view, I believe I may conclude: (1) If all cases of grave malaria are far from presenting atypical plasmodia, the existence, on the other hand, of abnormal hematozoa in the peripheral circulation signified nearly always: severe case. (2) Thus there is an obligation to sample the peripheral blood of all malarial patients, either proven or suspected, apyretic or febrile, treated with quinine or not. The examination of this blood would naturally be practiced with all necessary care and patience. (3) The existence of atypical forms of plasmodia makes mandatory, whatever the apparent clinical form of the attack, the re-enforcement of specific treatment."

THE BIOLOGIC ACTION OF ROENTGEN-RAYS IN TUBERCULOSIS. G. BRDICZKA, Beitr. z. Klin. d. Tuberk. **72**:298 and 312, 1929.

Thirty-one patients with pulmonary tuberculosis were treated with roentgen rays, and their blood pictures were determined at frequent intervals. Most

frequently, the patients reacted with a leukocytosis, but other types of reactions occurred in a considerable percentage of patients.

Normal and allergic guinea-pigs received intracutaneous injections of tubercle bacilli. Some of the resulting lesions were irradiated; others served as controls. Treatment with x-rays seemed to make no difference in the reinjection foci. In the primarily infected animals, the irradiated lesions formed larger abscesses than the controls.

MAX PINNER.

THE VIRULENCE OF B.C.G. O. KIRCHNER and E. A. SCHNIEDER, Beitr. z. Klin. d. Tuberk. **72**:673, 1929.

A strain of B.C.G. was transplanted in direct sequence into the cornea of ten successive rabbits. No increase in virulence was observed during this experiment, which lasted thirteen months. The reinoculation was always done before the corneal focus became vascularized. Foci produced by 0.0001 mg. developed more slowly but reached the same extent and healed much more slowly than foci produced by 0.001 mg.

MAX PINNER.

VIRULENCE AND TYPE OF BACILLARY STRAINS FROM CHILDHOOD TUBERCULOSIS. H. OPITZ and SHERIF, Beitr. z. Klin. d. Tuberk. **72**:523, 1929.

One bacillus of a virulent culture may produce generalized tuberculosis in guinea-pigs. According to the determinations on twenty-three strains, the virulence of the bacilli does not play a decisive rôle in childhood tuberculosis. Two of the twenty-three strains belonged to the bovine type, one was derived from a tuberculous peritonitis and one from a meningitis. The latter was probably associated with a strain of the human type.

MAX PINNER.

THE VIRULENCE OF TUBERCLE BACILLI IN PULMONARY TUBERCULOSIS. W. ROLOFF and W. PAGEL, Beitr. z. Klin. d. Tuberk. **72**:685, 1929.

Thirty-three strains of tubercle bacilli of the human type were isolated from sputum from different forms of pulmonary tuberculosis. Their virulence was tested by intracutaneous inoculation into guinea-pigs. The size and the development of the cutaneous focus made it possible to differentiate bacilli of higher and lower virulence, the former showing more histiocytic infiltration, ulceration and tubercle formation, while the latter showed more abscess formation. A relation between the virulence of the bacilli and the clinical course of the disease from which they were isolated was not apparent.

MAX PINNER.

IMMUNOLOGICAL STUDIES OF MONKEYS AFTER INOCULATIONS WITH B.C.G. F. GERLACH and R. KRAUS, Centralbl. f. Bakteriol. (Abt 1) **110**:179, 1929.

The authors injected B.C.G. into monkeys (*Macacus rhesus*) in amounts of from 30 to 50 mg. with no serious consequences, and observed the development of an immunity against later tuberculous infection to both the human and the bovine type of tubercle bacilli. The control monkeys under the same conditions developed a typical progressive tuberculosis. On the basis of these experiments, the authors conclude not only that progressive tuberculous processes resulting from virulent and pathogenic tubercle bacilli can give rise to an immunity to infection, but also that attenuated tuberculogenic but nonpathogenic strains of tubercle bacilli can confer immunity against virulent strains of both the human and the bovine type of tubercle bacilli.

PAUL R. CANNON.

THE NATURE OF THE TOXICITY OF MANNITE-FERMENTING DYSENTERY BACILLI. A. DE ASSIS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **58**:343, 1928.

The toxicity of a recently isolated Hiss Y type strain was tested by the intravenous injection of mice with four preparations: (1) old bouillon culture filtrate;

(2) filtrate of culture autolyzed in distilled water; (3) killed dried bacilli obtained by centrifuging a distilled water suspension; (4) wash water toxin, the supernatant of a centrifuged suspension of the bacteria dried, redissolved and centrifuged to clear of all insoluble material. Preparations 1 and 2 were nontoxic; 3 and 4 were toxic. Prolonged immunization of horses with these antigens gave negative results for antitoxin production. The author concludes that the toxicity of Hiss Y dysentery bacilli is bound up with the protoplasm and is not due to a toxin.

ROY C. AVERY.

Immunology

UNDULANT FEVER IN RELATION TO PREGNANCY AND ABORTION. E. L. CORNELL and C. R. DE YOUNG, *Am. J. Obst. & Gynec.* **18**:840, 1929.

Of 1,015 samples of serum from pregnant women in Chicago, none gave a definitely positive agglutination of *B. abortus* or *B. melitensis*. Five gave weak agglutinations. Of twenty-three serums from women who had aborted, one gave a reaction at 1:80.

INFLAMMATION AND IMMUNITY. EUGENE L. OPIE, *J. Immunol.* **17**:329, 1929.

The observations that have been described help to explain the changes that occur when an animal sensitized by infection with a suitable micro-organism is reinfected with the same agent. An inflammatory reaction of unusual intensity occurs and this reaction brings to the site of infection plasma containing antibodies. The experiments cited show that the two factors promote fixation and destruction of bacteria. Anaphylactic inflammation to which an animal repeatedly injected with foreign protein becomes susceptible protects the body from the injurious agent. The paradox between increased susceptibility to injury and the resistance of immunity is only apparent. The local injury that occurs is brought about not so much by the foreign agent introduced into the tissues, which, it is true, is fixed at the site of entry, as by the coming together of this antigen with antibody which is a product of immunization. The hypersensitiveness of infection, illustrated by the tuberculin reaction, is manifested by an acute inflammatory reaction that has all of the essential characteristics of anaphylactic inflammation. It has not been possible to demonstrate its relation to any antibody that finds its way into the blood serum but the evidence available does not exclude this relationship. The hypersensitiveness of infection that is usually manifested by reaction to products of the micro-organism concerned occurs under natural conditions in the presence of living bacteria that have invaded the body. The evidence I have cited shows that the acute inflammatory reaction produced in the sensitive animal by bacterial products retards bacterial invasion somewhat ineffectively at first, not only by bringing antibodies to the site of attack but by fixing bacteria at the site of entry so that they cannot enter the blood stream. Both with anaphylactic inflammation and with the inflammatory reaction of infected animals, vital organs are protected at the expense of local injury.

AUTHOR'S SUMMARY.

ISO-AGGLUTININS IN CATTLE. RALPH B. LITTLE, *J. Immunol.* **17**:377, 391, 401 and 411, 1929.

The examination of the blood from 209 cows and 31 bulls for hemagglutination is reported. The presence of iso-agglutinins in the blood of bovines is established. It is possible to identify three principal groups; however, the anomalous reactions shown by some serums suggest additional grouping. In certain bloods agglutinin as well as agglutinable substance is present in the blood of the same individual. The agglutinins are labile and disappear on standing at room or refrigerator temperature. So far the different blood types seem to bear no relation to the

various breeds of cattle. When group I serum is heated at 60 C. for one hour, the agglutinative substance is generally inactivated. A temperature of 56 C. for one hour is not sufficient to inactivate all serums completely. When group I serum is heated at 60 C., one component of agglutination is destroyed. With the addition of fresh unheated serum from certain cows, this component is again restored.

AUTHOR'S SUMMARY.

THE DICK TEST AND ALLERGIC SKIN REACTIONS TO STREPTOCOCCUS NUCLEO-PROTEINS. K. ANDO, J. Immunol. **17**:361, 1929.

From the Dick toxin two substances have been obtained with which skin reactions can be produced in human beings: a nucleoprotein and a specific toxin. The so-called nucleoprotein causes a skin reaction that cannot be distinguished from that caused by ordinary Dick toxin; it is heat-stable and nontoxic for man; it does not cause any skin reaction in white pigs. By repeated alcohol and acid precipitation a relatively pure specific toxin can be obtained from culture filtrates of *Streptococcus scarlatinae*; this causes reactions in the skin of human beings and white pigs; it is destroyed by heating to 80 C. for thirty minutes, and its action is neutralized by scarlatinal antitoxin. Susceptible persons can be immunized with it. In the course of immunization the scarlatinoid syndrome was observed in some cases. No evidences of allergy could be obtained with the true toxin-exotoxin, but the nucleoprotein gave rise to an allergic condition, and a skin reaction to the protein may be regarded as allergic. The nucleoprotein may influence the reaction to the ordinary Dick toxin, especially if it is weak in true toxin. High dilutions of potent toxin should be used preferably, and the Washington standard toxin was found to be very satisfactory as it contained traces only of nucleoprotein.

HORSE SERUM AS A HETEROPHILIC ANTIGEN. I. DAVIDSOHN and S. G. RAMSDELL, J. Immunol. **17**:365, 1929.

There are present in horse serum heterophilic antigens of the Forssman type, as shown by the development of a relatively strong antiship hemolysin in rabbits immunized with large quantities of the serum. Absorption with heterophilic organs removed the hemolysin, while absorption with nonheterophilic organs diminished its titer only slightly, possibly due to physical absorption. The immune serums did not contain agglutinins for sheep red cells, neither did they contain hemolysins and agglutinins for horse and guinea-pig red cells. Antistreptococcus serum has antigenic qualities similar to those of plain horse serum, while diphtheria globulin does not stimulate the production of heterophilic antibodies; and subcutaneous injection of any one of the three serums fails to call forth a response. The serums of rabbits, as a result of the treatment outlined, become toxic for the guinea-pig. This toxicity is shown to be not identical with the sheep cell hemolysin.

AUTHORS' SUMMARY.

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI. JAMES M. NEILL and WILLIAM L. FLEMING, J. Immunol. **17**:419, 1929.

The present example of diphtheria bacterial hypersensitiveness agrees with the previous examples in that it is manifested by an immediate skin reaction and in that the capacity for the reaction can be passively transferred. It differs, however, in that the individual is particularly reactive with a heat (60 C.) labile product not involved in the reactions of the previous diphtheria-sensitive persons. This product is apparently contained in effective concentration only in the unheated culture filtrates of toxicogenic diphtheria bacilli and not in the filtrates of non-toxicogenic strains nor in solutions of material derived from the washed bacterial cells. If it is not toxin, it is a hitherto unrecognized diphtheria bacterial product that possesses a degree of lability not usually encountered among the

bacterial substances associated with hypersensitive reactions. The results are discussed in respect to the possibility that the described reactions may represent an example of true hypersensitiveness of man to diphtheria toxin.

AUTHORS' SUMMARY.

THE INFLUENCE OF BLOCKADE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE FORMATION OF ANTIBODIES. P. R. CANNON, R. B. BAER, F. L. SULLIVAN and J. R. WEBSTER, *J. Immunol.* **17**:441, 1929.

The liberation into the blood stream of hemolysins to sheep's red corpuscles following blockading procedures depends on the manner of administration of the blockading material and the amount of antigen injected. Repeated injections of suspensions of india ink, particularly when given intravenously and continued after the injection of a small quantity of "tested-antigen," are followed by a significant decrease in the liberation of antibody into the blood stream, this liberation apparently varying inversely with the extent to which the phagocytic cells are blocked. This decrease in output of antibody is independent of individual variation of animals, loss of weight or of depression by fluids alone. Evidence is presented that small amounts of blockading material stimulate the liberation of antibody whereas large amounts tend to depress such a liberation. These experiments offer additional evidence that antibodies, at least hemolysins, are formed by the phagocytic cells of the mesenchymal tissues.

AUTHORS' SUMMARY.

THE SENSITIVENESS OF TUBERCULOUS GUINEA PIGS ONE MONTH OLD TO THE TOXICITY OF TUBERCULIN. JULES FREUND, *J. Immunol.* **17**:465, 1929.

The intracutaneous tuberculin test is negative or only very slightly positive in tuberculous guinea-pigs not more than 1 month old. Guinea-pigs of this age are about as sensitive to the toxin action of old tuberculin injected into the peritoneal cavity as adult tuberculous guinea-pigs. These experiments indicate that the mechanism that mediates systemic hypersensitiveness is fully developed in young tuberculous guinea-pigs at an age when the dermal reaction is very slight or negative.

AUTHOR'S SUMMARY.

ON THE NATURAL IMMUNITY TO SCARLET FEVER OF THE JAPANESE AND CHINESE RESIDING IN SOUTH MANCHURIA. K. ANDO, H. NISHIMURA and K. OZAKI, *J. Immunol.* **17**:473, 1929.

According to the Dick skin test there is a considerable difference in the susceptibility to scarlet fever between the Japanese and the Chinese residing in South Manchuria. The difference in scarlet fever morbidity of these two races may at least be partly explained by the difference in their susceptibility. No fact has been discovered which seems to indicate that there is a greater percentage of negative reactors among Japanese children who lived long or were born in Manchuria where scarlet fever is more prevalent than in Japan proper than among those who lived long in Japan proper and have immigrated only recently. It seems reasonable to suppose that the difference in susceptibility may indicate racial difference of "Antikörperbildungsbereitschaft" in the sense of Hirsfeld, but not dependent on the difference in "Umwelteinflüsse."

AUTHORS' SUMMARY.

ROCKY MOUNTAIN SPOTTED FEVER. A. L. KERLEE and R. R. SPENCER, *Pub. Health Rep.* **44**:179, 1929.

The serums from guinea-pigs inoculated with Rocky Mountain spotted fever virus did not agglutinate two strains of *B. proteus* X₁₀.

Serums from rabbits similarly inoculated with spotted fever virus showed a definite increase in agglutinin content reaching a maximum titer on the ninth day after onset of symptoms, or the fourteenth day after inoculation.

The serums of human patients taken during the course of the disease and during convalescence showed the presence of agglutinins for two strains of *B. proteus* X₁₂.

AUTHORS' SUMMARY.

POSTVACCINAL ENCEPHALITIS. E. GILDEMEISTER, *Centralbl. f. Bakteriol.* (Abt. 1) **110**:120, 1929.

This paper is a general discussion of the problem of postvaccinal encephalitis. The cases occurring particularly in Europe and England are reviewed and discussed. The view most stressed is that of the so-called activation theory; namely, that the vaccination activates an invisible virus already present in the body of the person vaccinated. No definite facts, however, are given to explain the phenomenon.

PAUL R. CANNON.

THE INFLUENCE OF THE RETICULO-ENDOTHELIAL SYSTEM ON INFECTION AND ANTIBODY FORMATION WITH VACCINE VIRUS. S. ZURUKZOGU and N. JOFFE, *Centralbl. f. Bakteriol.* (Abt. 1) **110**:220, 1929.

Guinea-pigs and rabbits were subjected to intravenous injections with india ink and then tested with vaccine virus to determine the effect on the local reaction and the formation of antibodies. The local reaction was less in the blocked animals than in the controls, whereas in the earlier periods, more virus was present in the blood stream of the blocked than of the control animals.

PAUL R. CANNON.

THE EFFECT OF ROENTGEN RAYS ON THE SPECIFIC IMMUNE BODIES. ALEXANDER LUSZTIG, *Centralbl. f. Bakteriol.* (Abt. 1) **111**:244, 1929.

The effects of roentgen rays on the specific antibodies depends on the intensity, the time of radiation with respect to the injection of the antigen and the individual reactivity of the animal. Thus, under certain conditions, there is an increased production of antibodies, while under others there is a reduction. The detailed results for various types of antibodies are given.

PAUL R. CANNON.

CHANGES IN THE RETICULO-ENDOTHELIUM OF THE LIVER, SPLEEN AND LYMPH NODES OF IMMUNE RABBITS. EMIL EPSTEIN, *Centralbl. f. Bakteriol.* (Abt. 1) **110**:223, 1929.

This is a morphologic study of the changes induced in the reticulo-endothelial cells of the rabbits immunized against swine serum, sheeps' red cells, etc., rather than against living infectious antigens. Thus, the changes are not complicated by the inflammation from infection. The experiments demonstrated particularly well in the liver an active proliferation of the cells of the reticulo-endothelial apparatus. The various types of such cells are described in detail and their possible sites of origin discussed. In the spleen and lymph nodes there was a marked proliferation of reticulum cells and a prominence of germinal centers in the malpighian bodies. He concludes that the noninfectious antigen acts on these cells of the histiocytic apparatus as an activating irritant, the cells reacting not only by proliferation but also by the secretion of antibodies.

PAUL R. CANNON.

ENCEPHALITIS FOLLOWING SMALLPOX VACCINATION. E. GILDEMEISTER, *Deutsche med. Wchnschr.* **55**:1372, 1929.

The spinal fluids from four patients with postvaccinal encephalitis were examined for vaccine virus by inoculation into the corneas of rabbits. In one patient the

spinal fluid taken on the seventh day after vaccination was found to contain the virus, while the spinal fluids of the other three taken from twenty to twenty-four days after vaccination produced no corneal reaction.

PAUL J. BRESLICH.

PROTECTIVE SUBSTANCES IN SYPHILIS. A. HAUPTMANN and A. GALLINEK, Klin. Wchnschr. 8:1485, 1929.

The effects of normal serum (with and without phagocytes) on spirochetes was compared under identical conditions with the effects of syphilitic and meta-syphilitic serum (with and without phagocytes). The serum of ten normal persons, of ten patients with secondary syphilis, of eleven patients with paralysis, and of two patients with cerebrospinal syphilis was tested against spirochetes, all but in the last mentioned from chancres of rabbits. There was no difference in the effects of serum with and without leukocytes. Lethal effects of the spirochetes began with normal serum after three hours and were completed after five hours. In half of the serums from patients with secondary syphilis these manifestations began in ten minutes, and after thirty minutes the spirochetes were dead. In the remainder of the serums from patients with secondary syphilis the lethal effects began after from one to one and one-half hours and were complete after from one and one-half to two hours. In only one serum were there higher values. The patient from whom this serum was obtained was found later to have received antisyphilitic treatment. The serum of paralytic patients reacted practically like that of normal persons. Lethal effects with serum from patients with cerebrospinal syphilis appeared in a short time. In these experiments spirochetes obtained from cultures were used. With leukocytes present in this series the spirochetes remained alive for a shorter time than in serum alone.

EDWIN F. HIRSCH.

THE PHYSIOLOGIC MALLEIN REACTION. H. BROKMAN and H. HIRSZFELD, Klin. Wchnschr. 8:1499, 1929.

The intracutaneous mallein test in a certain percentage of children is positive, and this percentage increases with age. The percentage range in the authors' series varies between 12.5 in the 0 to 1 year group and 42.3 in the 5 to 12 years group.

EDWIN F. HIRSCH.

THE NORMAL HUMAN ANTIBODY CURVE. E. FRIEDBERGER, G. BOCK and A. FÜRSTENHEIM, Ztschr. f. Immunitätsforsch. u. exper. Therap. 64:294, 1929.

The blood serum of various ages was studied with respect to its content in lysin for sheep corpuscles and agglutinin for rabbit corpuscles. No such antibodies were found in the blood of the umbilical cord at birth, but during the early years the content in antibodies rises, reaching the high point at the age of 10 years; the lysin now diminishes henceforth while the agglutinin remains high until about the thirtieth year when a gradual fall begins. There are individual exceptions to this general course. The content of the blood serum in the antibody bears no relation to the blood grouping. The course of the antibodies in question resembles that of diphtheria antitoxin, and it is suggested that the antitoxin curve is not due to infection but to the manifestation of a general biologic phenomenon.

Tumors

THE AGE INCIDENCE OF TUMORS IN MICE AND ITS INHERITANCE. L. J. TUREEN and LEO LOEB, J. Cancer Research 13:1, 1929.

The present detailed investigation by Tureen and Loeb is a painstaking analysis of the age incidence of tumors in mice. In this study as in those previously reported by Loeb, evidences are produced to show that there exists a

definite relationship between tumor age and tumor rate. In general, the higher the tumor rate, the earlier the tumors appear and the lower the tumor rate, the later they appear. The authors also found that in addition to this relation, there exists another factor, i. e., a specificity of the age incidence of tumors in certain strains. Thus, there are strains with a high tumor rate which do not appear as early as certain other strains with a tumor rate not higher than they have. In certain cases strains with a low tumor rate may show an early tumor age due to the fact that a substrain may differ from the parent strain in the tumor rate but may inherit its characteristic tumor age. These two factors, according to the authors, interacting with each other, determine the age incidence of tumors in mice. Tureen and Loeb go into details concerning the strains with high, medium and low tumor rates, as to their age incidence of tumors.

B. M. FRIED.

SKIN LESIONS AMONG TAR WORKERS. H. B. WOOD, *J. Cancer Research* **13**: 54, 1929.

Wood investigated the direct effect of tar on 88 tar handlers in municipal gas works, in coke by-products plants and in plants making briquettes. As a result of his investigation he found that workmen handling coal tar developed tar warts. Low temperature, distillate tar and petroleum tar, respectively, did not have any irritating action on the human skin.

B. M. FRIED.

AGGLUTINATION PHENOMENA IN CANCER. N. WATERMAN and L. DE KROMME, *J. Cancer Research* **13**:60, 1929.

The authors produce evidence to show that in man, mouse, rat and rabbit, there normally exists agglutinins for tumor cells. The property of agglutination goes hand in hand with the cytolytic properties of human serum toward neoplastic cells as demonstrated by Freund and Kaminer. It is interesting that umbilical cord serum lacks the properties of agglutination and of cytolysis of tumor cells. It is likely that these "factors" are acquired during extra-uterine life.

B. M. FRIED.

A CRITICAL SURVEY OF EPITHELIAL TUMORS OF THE APPENDIX. A. A. THIBAUDEAU and E. M. BURKE, *J. Cancer Research* **13**:73, 1929.

In a review of 3,746 appendixes the authors have found 19 epithelial tumors in the appendix and adjacent small intestine, 12 of which were of the carcinoid type. In their material there was no definite connection between the tumor and the epithelium of the mucous membrane. The tumors did not recur after removal. They are not always associated with inflammatory changes in the appendix or intestine.

B. M. FRIED.

TRANSPLANTATION STUDIES ON TUMORS ARISING SPONTANEOUSLY IN HETEROZYGOUS INDIVIDUALS. LEONELL C. STRONG, *J. Cancer Research* **13**: 103, 1929.

According to the genetic theory devised by Strong, the fate of the implanted tumor tissue when placed in a given person (host) is brought about by a reaction between the host (determined by its genetic constitution) and the transplanted tumor cell (controlled by its genetic constitution). Tumor cells possess a specific individuality which is self-regulating, being transmitted from one cell generation to the next through the process of cell division.

In the present elaborate experiments Strong demonstrates the fact that the growth of an implant in a given person is controlled by the activity of certain physiologic host determiners derived from the zygote that gave rise to the person. In every case investigated in controlled stock the susceptibility and immunity to the implant were definitely inherited according to Mendelian principles. Trans-

mission of susceptibility to the growth of the implanted tissue has always followed the laws of Mendelian heredity. The simultaneous functioning of dominant multiple factors has ever been the type of inheritance, except in one case.

The author is of the opinion that the problem of neoplastic tissue is a problem of genetics and may eventually be solved by genetic methods. He believes that it is permissible to expect that by the use of the transplantation method, together with a full appreciation of genetic principles, some light may be thrown on the problem of the conversion of normal tissue into the neoplastic type.

B. M. FRIED.

A STATISTICAL STUDY OF THE OCCURRENCE OF CANCER AND TUBERCULOSIS IN 11,195 POST MORTEM EXAMINATIONS. H. A. CARLSON and E. T. BELL, *J. Cancer Research* **13**:126, 1929.

Active tuberculosis is much less frequent in cancerous than in noncancerous subjects, and cancer is much less common in those with active tuberculosis than in those with no tuberculosis or with healed tuberculosis. But active tuberculosis is even less frequently associated with heart disease than with cancer, and cancer shows less association with heart disease than with active tuberculosis.

These results do not mean that active tuberculosis inhibits the development of both cancer and heart disease. They are due to the fact that the majority of persons with active tuberculosis have no other major illness and therefore the control (noncancerous, without heart disease) must always have a higher percentage of tuberculosis.

The authors did not find any statistical evidence to support the view that there is an antagonism between cancer and tuberculosis.

The only proper control for the association of active tuberculosis and cancer is the incidence of active tuberculosis in some other disease.

AUTHOR'S SUMMARY.

ON REGRESSION IN TRANSPLANTED TUMORS IN MICE FREED OF WORMS. MILLARD C. MARSH, *J. Cancer Research* **13**:136, 1929.

A mammary tumor spontaneous in albino mice has been propagated in long inbred individuals of the strain in which it arose. These mice have a chronic infestation, which extends indefinitely through ancestral generations, with intestinal nematodes, besides sporadic cestodes. Regression of the transplanted tumor is low.

A colony of mice from this strain was segregated and kept free from intestinal helminths during four years and thirteen generations of continued inbreeding. In these mice regression of the transplanted tumor is high. The difference appears mathematically significant.

AUTHOR'S SUMMARY.

BLOOD CHOLESTEROL STUDIES IN CANCER. W. L. MATTICK and K. W. BUCHWALD, *J. Cancer Research* **13**:157, 1929.

There is a tendency in cancer to a hypercholesterolemia in the plasma, with little change in the corpuscles. Lecithin fails to show significant changes except for slightly lower values in the plasma. Total fatty acids show the most marked changes, being especially higher than normal values in the plasma, with a lesser but similar tendency in the corpuscles. From the authors' work it would appear that in cancer either fat absorption is increased or the utilization is decreased, with resulting accumulation of total fatty acids and fats, especially in the plasma.

B. M. FRIED.

ON TRUE MIXED CARCINOMATOUS AND SARCOMATOUS TUMORS (SARCO-CARCINOMA) WITH REPORT OF A MIXED CARCINOMA-CHONDROSARCOMA OF THE THYROID OF A DOG. ROBERT MASON and H. GIDEON WELLS, J. Cancer Research **13**:207, 1929.

The authors report a case of a large mixed tumor arising in the thyroid of a dog. This consisted of a mixture of adenocarcinoma with osteoid sarcoma. There were many metastases in the lungs, some consisting solely of carcinoma, some solely of osteoid sarcoma and some presenting a mixture of both elements.

B. M. FRIED.

ENTDIFFERENTIATION OF PRIMARY CARCINOMA OF THE BRONCHI AND LUNGS. CARL VERNON WELLER, J. Cancer Research **13**:218, 1929.

Weller investigated fourteen primary pulmonary cancers, thirteen of which were found in a series of 3,000 necropsies. In no instance could he trace the origin of the tumor from the "alveolar epithelium." It seemed clear that all types of carcinoma of the lung can take origin from bronchial structure.

The histologic picture of a particular neoplasm or of a particular portion of a neoplasm depended on the degree of entdifferenciation and should not, therefore, be used to determine histogenesis. The author gives a histologic description of the fourteen bronchiogenic tumors with an ingenious attempt to correlate the various forms of carcinoma on a biologic basis.

B. M. FRIED.

NO LEAD IN TUMOR TISSUE AFTER INTRAVENOUS INJECTION OF COLLOIDAL LEAD. M. C. REINHARD AND K. W. BUCHWALD, J. Cancer Research **13**:239, 1929.

In order to determine the quantity of lead deposited in tumor tissue following the intravenous injection of colloidal lead, the authors used mice bearing spontaneous tumors. They used the commercial lead diaspore or colloidal lead phosphate. The chemical was injected intravenously. With the method used, they failed to reveal any traces of lead in the tumor tissue.

B. M. FRIED.

CARCINOMA OF THE CERVIX UTERI AND RELATION BETWEEN THE HISTOLOGICAL STRUCTURE AND THE RESULTS OF RADIATION. A. A. THIBAudeau and E. M. BURKE, J. Cancer Research **13**:260, 1929.

The authors attempted to correlate the clinical evidences of malignancy by a given tumor with the histologic characteristics as revealed on microscopic examination. For that purpose they investigated twenty-eight cases of epithelioma of the cervix uteri for which the patients were successfully treated by irradiation and which have shown no evidence of recurrence for more than five years.

Their conclusions are that histologic grouping and indexes of malignancy are of limited value in prognosis in cases of epithelioma of the cervix uteri.

B. M. FRIED.

LACTIC ACID FORMATION IN TUMOR TISSUE. HELEN R. DOWNES, J. Cancer Research **13**:268, 1929.

The study by Downes is concerned with the investigation of the lactic acid-forming ability of several different kinds of human tumors and of transplanted animal tumors. The results obtained yielded "neither confirmation nor disproval of Warburg's contention."

B. M. FRIED.

CARCINOMA GELATINOSUM OF THE PROSTATE. A. KLISSUROW, Virchows Arch. f. path. Anat. **268**:515, 1928.

This type of prostatic tumor is rarely observed. The microscopic examination showed large masses of mucoid material with islands or strands of carcinoma cells here and there.

K. Hosoi.

INNERVATION OF TUMORS. E. HERZOG, Virchows Arch. f. path. Anat. **268**:536, 1928.

The innervation of 100 benign and malignant tumors and metastases was studied by means of the modified Bielschowsky method to bring out the axis cylinders of the nerves. In the majority of the tumors, nerves were frequently found in the stroma if the growth was not circumscribed. In all primary tumors with well defined borders, benign as well as malignant, nerves were never found. This was found to be true also in circumscribed metastases of carcinoma. Signs of proliferation of the nerves were seldom observed. The various structures described by others as nerve end apparatus most likely are a sign of regeneration. The relationship of the nerves to the tumor cells in the form of a specific nerve end apparatus was not observed.

K. Hosoi.

MALIGNANT UTERINE CHORIO-EPITHELIOMA. R. MEYER, Ztschr. f. Geburtsh. u. Gynäk. **92**:259, 1927.

Conclusions are drawn from twenty-eight cases of chorio-epithelioma uteri. The tumor originates from fetal epithelial cells of the normal placenta at different periods, or from rests of hydatiform moles of different age and after longer or shorter retention. Chorio-epithelioma of long latency either is not recognized in time on account of slow growth (but not more than one or two years after the last pregnancy) or more frequently a more recent, abortive pregnancy is overlooked. Chorio-epithelioma observed late after menopause represents an incorrect histologic diagnosis. A chorio-epithelioma has no stroma of its own. The tumor cells proliferate under preservation of the cytolytic qualities of the normal chorionic cells. The maternal tissue may react against their growth by coagulation of the tissue, a process affecting also the tumor cells, or it cannot resist these cells and the tumor cells then dissolve the maternal cells. Transitional conditions may exist in the individual tumors. The causal genesis is unknown. The proliferation of lutein cells and the formation of ovarian cysts are secondary to the tumor formation. They are moreover absent in early cases and in old women. They may undergo spontaneous regression after removal of the hydatiform mole or the chorio-epithelioma. Surgical trauma represents a doubtful contributory factor. Over-nourishment of chorionic epithelial cells which became separated from the ovum is one of the blastogenic factors. The histologic diagnosis is not always possible, especially not during the first two months of pregnancy, as the ovum possesses at that period a trophoblastic membrane with numerous masses of proliferating chorio-epithelial cells. Even the histologic evidence of lysis of maternal tissue may represent a physiologic process at that time. A positive diagnosis from the histologic examination alone is impossible during this period. The tumor follows usually a hydatiform mole when it occurs in this period. A positive diagnosis is justified only if there is a marked proliferation of chorio-epithelial cells. After the second month a large mass of chorio-epithelial cells in uterine tissue is indicative of malignancy. Hydatiform mole is an abnormal proliferation of chorio-epithelial cells which is more marked at an early stage than in a late one. Its persistence is suggestive of malignancy. The diagnosis of a malignant condition is more difficult if a hydatiform mole is present than if it is not. Chorionic epithelial cells surrounded by fresh maternal blood stay alive. These cells, located intravascularly deep in the muscle, represent a factor of steadily increasing danger in

regard to malignant transformation, metastases and ectopic malignant transformation of these cells. In the presence of villi the prognostic evaluation of the epithelial proliferation rests first with the evidence of tissue destruction, secondly with the unusual amount of chorio-epithelial cells and with the presence of atypical forms. But atypical forms alone are not indicative of malignancy as they may be due to the continuous fresh blood supply which results in a hypertrophy of the cells. The existence of destruction of maternal tissue and its lysis is, however, an absolute proof of malignancy. The presence of tissue coagulation cannot be used in the interpretation of the histologic observations. Especially does the presence of large masses of syncytial cells point to malignancy. The stroma of the villi does not furnish any evidence for the diagnosis. The diagnosis of a malignant condition can often only be made with due consideration of all clinical as well as pathologic observations. The diagnosis is difficult, requires great experience and cannot always be made. Every hemorrhage after delivery, abortion and especially after hydatiform mole has to be regarded as suggestive of chorio-epithelioma. Histologic examination of all tissue removed or expelled under such circumstances is absolutely indicated and necessary. Nodes in the visible genital sphere are always suggestive of metastases. Metastases have to be regarded as malignant even if they do not show destructive growth. Curettage of the uterus may be ineffective in chorio-epithelioma if the tumor is located in the uterine wall. Repeated examinations of the uterus and ovaries are indicated for several months following removal of a hydatiform mole. Subsequent irregular hemorrhages demand curettage and histologic examination of the removed tissue. Benign metastases exist in hydatiform mole. They consist always of villi. The early surgical removal of a chorio-epithelioma gives the best curative results. The extirpation has to be carefully done to prevent the production of operative traumatic metastases.

W. C. HUEPER.

Medicolegal Pathology

CARBON TETRACHLORIDE POISONING WITH MACROSCOPIC FAT IN THE PULMONARY ARTERY. H. E. MACMAHON and SOMA WEISS, *Am. J. Path.* **5**:623, 1929.

The gross and microscopic observations are described in an unusual case of carbon tetrachloride poisoning in which the blood in the right side of the heart and larger pulmonary arteries contained an extremely high percentage of fat (60 per cent). The severe damage to the liver, which was already large and filled with fat, was the probable source of the fat in the vascular system. Fat droplets that were small enough to pass through the capillaries of the lung and to gain entrance into the capillaries of other organs produced no microscopic lesions in either the heart, brain or kidney. It appears from these observations that the sensitiveness of alcoholic patients to carbon tetrachloride is increased not only because of increased absorption of the drug, as well as the synergistic action of alcohol and carbon tetrachloride together in producing liver damage, but also because of the possible presence of preexisting liver damage.

AUTHORS' SUMMARY.

ACUTE YELLOW ATROPHY OF THE LIVER DUE TO ACETYLENE TETRACHLORIDE. W. SCHIBLER, *Schweiz. med. Wchnschr.* **59**:1079, 1929.

Several cases of jaundice developed in workers in a shoe factory in which glue containing acetylene tetrachloride was used. In three cases death occurred. A detailed description is given of two of these cases in which acute yellow atrophy of the liver was present.

TATTOOINGS IN CRIMINALS: DIAGNOSTIC VALUE. PIETRO BIANCONI, Arch. di antrop. crim. 49:66, 1929.

According to the Lombrosian school, tattooings not only contain important data for identification but invariably indicate a decreased cutaneous sensibility toward pain, peculiar to many criminals. Tattooings often disclose some important psychologic characteristics pertaining to the intelligence and to the sentimental and emotional life of the delinquent, and they may yield valuable information about the life of the criminal. Some tattooings betray criminal attitudes and tendencies, and thus illustrate the dangerousness of the persons. Nearly all tattooings are manifestations of an inferior and atavistic psyche, tending to materialize a dominant idea in the form of a symbol, which uncovers and represents the delinquent's way of feeling and simultaneously expresses a more or less pronounced imprudence. In two cases of offenses against property the tattooings are minutely described and psychologically interpreted.

E. L. MILOSLAVICH.

SUBEPICARDIAL ECCHYMOSES IN ACUTE ASPHYXIA. FRANCESCO BALLOTTA, Arch. di antrop. crim. 49:503, 1929.

Following the observations of Bichart, Tullio and Businco have recently shown by roentgenographic and cinematographic studies that during asphyxiation the heart dilates, at times to such a degree that it appears twice as large as under normal circumstances. The author studied the development of subepicardial ecchymoses, using the technic of these investigators. He confirms the observations of Hofman that minute petechial hemorrhages are found regularly in the asphyxiated newborn but are rare in adults. In experiments on rabbits and dogs Ballotta observed that at the beginning of asphyxiation the heart shows a decrease in size. This stage is followed by enlargement to about twice the normal size, occurring during the twenty-fifth to the thirtieth second of asphyxiation and lasting for approximately 20 seconds. Particularly the right ventricle seems to become dilated. Then a decrease in the volume of the heart again occurs. Subepicardial ecchymoses are not present. When the heart enlarges, during the stage of the acute asphyxia, its vessels also show dilatation and engorgement but do not rupture. However, subepicardial hemorrhages develop if the wall of the blood vessel possesses an insufficient elasticity. In the new-born, the vascular elastic apparatus is not yet completely developed, and in adults the wall of the vessel may be diseased. The occurrence of subepicardial hemorrhages depends, therefore, on the structural condition of the walls of the blood vessels.

E. L. MILOSLAVICH.

Technical

A STUDY OF STOOLS CULTURED FOR *ENDAMEBA HISTOLYTICA* FOR DIAGNOSTIC AND OTHER PURPOSES. CARLO J. TRIPOLI, Am. J. M. Sc. 178:822, 1929.

The cultural method of stool examination here described for the diagnosis of the presence of *Entameba histolytica* has so far been equal to any laboratory means of diagnosis and may eventually prove superior to the direct microscopic method. It is thought that the use of the cultural method of stool examination will result in a considerable saving of time and personnel in public health work in the detection of carriers.

JOHN PHAIR.

AN EVALUATION OF THE LEUKOCYTIC REACTION IN TUBERCULOSIS. E. M. MEDLAR, Am. Rev. Tuberc. 20:312, 1929.

There is no specific leukocytic reaction in the tuberculous patient, and the use of the leukocytic formula is impossible as a diagnostic aid. The leukocytes may merely indicate that something abnormal is happening within the body. The

establishment of the clinical diagnosis of tuberculosis is necessary before the leukocytes can be of aid in the interpretation of the status of the tuberculous process. One may then interpret the leukocytic picture on the basis of the rôle that each leukocytic type plays in the pathogenesis of tuberculosis. The leukocytic reaction often agrees closely with the clinical status of a tuberculous person but at times there is a marked disagreement and then the leukocytes indicate the actual status of the tuberculous process more accurately than does the clinical condition of the patient. The leukocytes indicate only the status of the tuberculous process at the time the blood is obtained and therefore blood counts at relatively frequent intervals are necessary to determine the trend of the disease. It is essential that the total leukocyte count, together with the differential percentages, be used if the maximum information is to be obtained from a leukocytic reaction in a case of tuberculosis. The neutrophil plays the chief rôle in tuberculous abscess formation and in the extension of tuberculous ulcers. The mononuclear leukocyte is the chief cell in new tubercle formation, and the lymphocyte predominates when a tuberculous lesion is healing. No definite rôle can be ascribed, at present, to the eosinophil or basophil.

H. J. CORPER.

PHOTO-ELECTROMETER WITH ONE STAGE OF AMPLIFICATION AS APPLIED TO THE DETERMINATION OF HEMOGLOBIN. CHARLES SHEARD and A. H. SANFORD, *J. A. M. A.* **93**:1951, 1929.

The authors present the following: A description of a modification of our original photo-electrometer used as a photo-electric hemoglobinometer, in which we have employed one stage of amplification and used a micro-ammeter for the measurement of the current in the photo-electric cell produced by the illumination from a constant source of light which passes through a selective absorptive filter and a specified dilution of blood; the portability of the instrument and the accurate and rapid determination of hemoglobin expressed in grams for each hundred cubic centimeters of blood, which recommend the photo-electric hemoglobinometer as an instrument of value in the routine examination of a large number of samples of blood and in research work; complete details regarding the *modus operandi* of the photo-electrometer; the theoretical considerations involved in photo-electric photometry as applied to the determination of hemoglobin, indicating that the readings on the instrument follow the laws of Lambert and Beer, in that the concentration of hemoglobin, as determined by the transmission of light in an absorption zone of oxyhemoglobin (beta band), is proportional to the negative logarithm of the unabsorbed light; experimental data obtained by the van Slyke, spectrophotometer and photo-electric hemoglobinometer and their comparison together with a determination of the absorption ratios spectrophotometrically (at 540 millimicrons) and by use of the photo-electric hemoglobinometer, a selective filter transmitting light only in the region of the beta absorption band of oxyhemoglobin being used; data substantiating the belief that the photo-electric hemoglobinometer, with one stage of amplification, will permit of the determination of grams of hemoglobin for each hundred cubic centimeters of blood within an average of 2 per cent of the van Slyke values, which have been taken as standards; the applicability of the principles of photo-electrometry to the determination of amounts of various unknowns in true or colloidal solutions, provided the unknown substance in solution possesses at least one characteristic absorption band for which a spectral filter, transmitting radiant energy only in the specified region, can be made.

AUTHORS' SUMMARY.

INFLUENCE OF FORMALIN FIXATION ON THE LIPIDS OF THE CENTRAL NERVOUS SYSTEM. ARTHUR WEIL, *J. Biol. Chem.* **83**:601, 1929.

1. The present opinion that solutions of formaldehyde are a fixative for the preservation of lipids should be revised.

2. In a 10 per cent solution of formalin (4 per cent solution of formaldehyde) the phosphatides are hydrolyzed, and the liberated phosphoric acid is found in a water-soluble composition in the fixing fluid. This process of decomposition proceeded gradually and was still found after ninety days' fixation.

3. Cholesterol and galactolipids (cerebrosides) are not appreciably changed. Consequently the resulting mixture of lipids after fixation in formalin contains more galactolipids than the original tissue.

4. The preservation and relative increase of galactolipids in formalin-fixed tissue have been utilized to explain some empirically known histologic facts; namely, the effect of pyridine in silver staining methods of nerve fibers and the staining and physical qualities of areas of so-called "mucoid degeneration" which are found in formalin-fixed material after treatment with alcohol.

AUTHOR'S SUMMARY.

THE DEMONSTRATION OF TUBERCLE BACILLI IN THE NEGATIVE SPUTUM OF TUBERCULOUS PATIENTS BY THE METHOD OF SCHILLER. R. MICHEL, *Beitr. z. Klin. d. Tuberk.* **72**:513, 1929.

This method yields more positive results than the usual methods of concentration, but fewer than cultural methods.

MAX PINNER.

PURE CARBON MONOXIDE GAS AS A BLOOD AND TISSUE-PIGMENT FIXATIVE. J. KERNER, *Centralbl. f. allg. Path. u. path. Anat.* **46**:5, 1929.

Kerner prepares gross specimens of fresh tissue as for permanent mounting, suspends them in a bell jar into which pure CO is put and thus preserves the natural coloration. The final results were undistinguishable from those obtained by the standard, slower fixatives of Kaiserling, Melnikow-Raswedenkow Pick or Jores. Subsequent preservation in formaldehyde or glycerin solutions does not affect the colors.

GEORGE RUKSTINAT.

CULTIVATION OF THE TUBERCLE BACILLUS BY THE METHODS OF UHLENHUTH AND HOHN. GERHARD ORZECZOWSKI, *Centralbl. f. Bakteriologie (Abt. 1)* **111**:362, 1929.

The method of Hohn yielded 96 per cent of positive cultures of tubercle bacilli, as against 39 per cent with the method of Uhlenhuth, in seventy-five sputums containing tubercle bacilli. For the microscopic examinations, however, the former method is not so satisfactory as the method of Uhlenhuth.

PAUL R. CANNON.

THE APPLICATION OF HOHN'S METHOD FOR THE CULTIVATION OF TUBERCLE BACILLI IN SANATORIA. K. KRAUSE, *Ztschr. f. Tuberk.* **54**:227, 1929.

This culture method yielded positive results in 23.4 per cent of 120 microscopically negative specimens of sputum.

MAX PINNER.

THE PRACTICAL SIGNIFICANCE OF TUBERCLE BACILLUS CULTURES FROM SPUTUM. H. SCHULTE-TIGGES, *Ztschr. f. Tuberk.* **54**:230, 1929.

Hohn's method for the isolation of tubercle bacilli yields many more positive results than bacterioscopic examination, but it is not as reliable as inoculation into animals.

MAX PINNER.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF GENITO-URINARY SURGERY

Stated Meeting, March 6, 1930

JOHN A. HARTWELL, *Presiding*

CLINICAL APPLICATIONS OF THE STRUCTURE OF TUMOR OF THE BLADDER. PAUL W. ASCHNER.

This study was made on 285 cases of vesical neoplasm submitted to biopsy or operation at the Mount Sinai Hospital since 1911. The classification employed is in accord with the general principles of tumor terminology and meets the clinical requirements in that it takes cognizance of gross as well as microscopic criteria. It is as follows:

- I. Papilloma (benign) cell uniformity and typism
 - Pedunculated: single
 - multiple
 - Sessile: papillomatosis
- II. Papillary carcinoma
 - Noninfiltrating: (a) scattered areas of somewhat atypical cells
 - (b) more diffuse, more marked atypism
 - Infiltrating: (c) cells of benign type (rare)
 - (d) cells anaplastic; stroma or stalk invasion
 - (e) cells anaplastic; submucosal or base invasion
 - (f) cells anaplastic; muscularis and perivesical invasion
- III. Nonpapillary (flat) carcinoma
 - (a) fibro (scirrhous)
 - (b) medullary (transitional cell)
 - (c) adeno
 - (d) squamous
 - (e) hornifying

There were two chief objects of the study, to evaluate the biopsy for diagnosis and to evaluate the structure in relation to prognosis.

The biopsy material is obtained with a rongeur forceps through the cystoscope. It is important to obtain material from different parts of the tumor and from various tumors when they are multiple. Tissue removed with the fulgurating electrode is unsatisfactory. The material must be studied with great care and attention to details, and with a mental attitude of "guilty until proved innocent."

In 242 cases the biopsy diagnosis rendered was correct in all but twelve, or 95 per cent. In reviewing these twelve cases, seven were found to be true errors, which could have been avoided. Therefore, the biopsy is potentially reliable in 97.5 per cent of cases (table 1).

TABLE 1.—*Papilloma Biopsy Reports Confirmed, Ninety Cases*

Number of Tumors in Bladder	Confirmed by Early Cystoscopic Control	Confirmed by Operative Specimen	Confirmed by Cystoscopic Control (1 to 15 Years)	Confirmed by Late Letter Control	New Tumors or Recurrences, Benign, Only 23 per Cent
Single, 56 cases.....	29	6	26	1	12
Multiple, 25 cases.....	14	4	9	..	7
Papillomatosis, 9 cases	1	5	5	2*	2

* One autopsy five years after cure.

The sources of error in biopsy diagnosis are:

1. Insufficient material or improper material.
2. Rare cases of infiltrating tumors of benign cell type (IIc).
3. Co-existence of benign and malignant growths in the same bladder.
4. Malignant cell changes confined to inaccessible depths of the tumor.
5. Cases of papillomatosis.

It is of the utmost importance that biopsy be made before resorting to treatment for suspected malignancy because inflammatory lesions may closely simulate cancer. Failure to do this has led to harmful radical surgical intervention.

TABLE 2.—End-Results in One Hundred and Eighty-Two Patients with Tumors of the Bladder

	Cases Followed-up	Number Arrested	Percentage Arrested
Papilloma.....	60	48	80
Papillary carcinoma, noninfiltrating	21	9	43
Papillary carcinoma, infiltrating....	71	13	18
Nonpapillary carcinoma.....	30	5	16

TABLE 3.—Summary of Two Hundred and Eighty-Five Cases Studied

Type of Tumor	Number of Cases	Biopsy Done	Biopsy Errors	No Treatment	Cystoscopic Treatment	Operative Treatment	Operative Treatment plus Radium	Operative Deaths	Deaths Due to the Disease	Deaths Due to Other Causes	Benign Recurrence	Malignant Recurrence	Metastasis	Number of Cases Followed-Up	Number of Cases Arrested	Percentage Arrested
Papillomas.....	91	90	0	..	71	23	..	3	..	4	22	1	..	60	48	80
Papillary carcinoma.....	138															
Noninfiltrating.....	30	25	3	5	9	11	5	3	5	4	1	2	2	21	9	43
Infiltrating.....	108	84	7	20	13	63	24	9	35	7	2	15	11	71	13	18
Nonpapillary carcinoma.....	44	35	0	10	1	29	4	9	13	1	..	9	6	30	5	16
Cases 6, 7, 9 and 10.....	..	4	2													
4 cases prostatic carcinoma.....	..	4	0													
1 myosarcoma.....	..	4	0													
1 adenoma.....	..															
1 carcinoma in scar after operation elsewhere	..															
1 fibroma.....	..															

Microscopic evidence of infiltration is found in 78 per cent of papillary carcinomas, whereas clinical signs of infiltration are observed in only 50 per cent. Resection should therefore include the full thickness of the wall of the bladder despite the absence of gross infiltration, whenever the biopsy reports papillary carcinoma and surgical intervention is resorted to. Failure to do so has resulted in early recurrence.

In 182 cases the termination of the case is known or a follow-up of three years is available. Cases with negative cystoscopy and with no evidence of metastasis are considered arrested. The results appear in tables 2 and 3.

Concerning prognosis, the following can be deduced: If cytologic criteria alone indicated prognosis, there should be a marked difference between groups IIa and IIb, but the percentage of arrested cases was 44 and 42, respectively.

If infiltration of the wall of the bladder indicated prognosis, then groups IIc and III should show similar results, which is the case, the result being 14 and 16 per cent.

In comparing noninfiltrating papillary carcinoma (groups IIa and b) with infiltrating papillary carcinoma (groups II, c, d, e and f), the percentage of arrested cases is 43 and 18, respectively.

Papillomatous cases are treacherous; of thirteen, four eventually proved malignant.

Conclusions.—Reliable information as to the nature of tumors of the bladder is obtainable by cystoscopic biopsy in 97.5 per cent of cases. The unavoidable failures occur chiefly in multiple tumors and papillomatosis.

Prognosis cannot be made from biopsy material alone in cases of malignancy.

A biopsy diagnosis of malignancy in a case simulating papilloma by cystoscopy and response to fulguration is a signal for more radical therapy (radium or surgical intervention).

Tumors of the bladder may be classified in a manner harmonious with general tumor terminology and with clinical requirements. They are benign or malignant.

Classification based on cell grading alone is not as practical for clinical purposes, and prognosis on such a basis does not coincide with the late results in this series of cases.

The presence or absence of infiltration appears to be a more reliable guide to the gravity of the situation.

The site of the malignant tumor determines its resectability and thus influences prognosis materially.

If a biopsy diagnosis of carcinoma is made and the case is considered surgical, segmental resection of the whole thickness of the wall of the bladder is the procedure of choice. Failure to do so even in the pedunculated tumors has often resulted in recurrence. Stalk invasion and tumor cells in blood vessels at the base cannot be detected by gross inspection.

As only thirty of 138 papillary carcinomas showed no evidence of infiltration, it is probable that types IIa and b represent an earlier stage in the development of the disease. Although histologic studies tempt one to believe that papillary carcinoma develops from papilloma in a considerable percentage of cases, the clinical evidence thereof is equivocal.

Before undertaking radical surgical intervention for tumor of the bladder a biopsy should be made, as other lesions may resemble neoplasm very closely.

A CONSIDERATION OF THE SURGICAL PROCEDURES IN THE TREATMENT FOR MALIGNANT DISEASE OF THE BLADDER. VERNE C. HUNT (Rochester, Minn.).

Considerable uniformity of opinion exists regarding the treatment for small single or multiple more or less superficial malignant lesions of the bladder. For the most part, such lesions have been and are at the present time successfully treated by transurethral electrocoagulation. Occasionally, however, there is failure of response to such treatment and other therapeutic agents as are applied to the larger and infiltrating lesions must be resorted to.

As yet there is still a justifiable conflict in the opinions regarding the relative merit of the physical agents and surgical procedures in some of the extensive malignant lesions of the bladder, and it is probable that in some instances the greatest prospects of cure and of palliation in the truly inoperable lesions may be expected through the combined use of both.

Experience has shown that some of the physical agents have been more effective in the treatment for the highly malignant lesions because of their greater radio-sensitivity than the lower grade lesions. Other factors influence the results of treatment, however, not least of which is the extent of involvement. The lower grade lesions are often more or less superficial, while those of higher grade often infiltrate the entire thickness of the wall of the bladder with extravascular extension. Experience has shown that purely on the basis of the degree of malignancy one may be guided as to the justifiable magnitude of a contemplated surgical procedure, for with a given degree of involvement, the justifiable magnitude of surgical procedure is greater for the lower grade than for the higher grade

malignant lesion. At the present time, bearing in mind the optimism possessed by some regarding the results of treatment by physical agents, I am of the opinion that an operable malignant lesion of the bladder is a surgical lesion and is most successfully dealt with by surgical procedures.

It may legitimately be asked: What are the prospects of cure of malignant lesions of the bladder? A definite prognosis for a malignant lesion anywhere in the body in the individual case is practically impossible to make, and prognosis may be made only in general on the basis of previous experience. Recently and elsewhere I reported the results obtained in the surgical treatment of 370 patients with graded epithelioma on whom all operations were done as procedures curative in purpose as opposed to palliative measures. In brief, and in general, the results showed that irrespective of the size or situation of the lesion or the magnitude of the operation, 65 per cent of the patients on whom radical operations had been performed for lesions graded 1 and 2 lived three or more years without recurrence, as opposed to 34 per cent in whom the lesions were graded 3 and 4 who lived three or more years without recurrence. When results were determined according to the site of the lesion, it was found that those following operations on the base of the bladder were not as good as those for lesions in the lateral walls and dome. Actually, the results showed that nearly 50 per cent more patients with lesions of the lateral walls and dome survived the three year period without recurrence than those who had been operated on for lesions of the base.

Surgical Procedures.—In a recent review of the surgical procedures employed during the years from 1925 to 1929 inclusive, in 256 cases of malignant lesion of the bladder at the Mayo Clinic it was found that in seventy-seven cases, or 30 per cent, the lesions were inoperable to any procedure that might be considered curative in purpose. This includes patients in whom a cystostomy was done as a palliative procedure and those cases in which inoperability was ascertained on exploration, but does not include such cases as were clinically hopeless and in which not even palliative cystostomy seemed justifiable. It is noteworthy that an additional seventy-eight cases were inoperable to the usual strictly surgical procedures of resection and excision, and comprised a group in which surgical diathermy, cautery destruction and transplantation of the ureters and cystectomy were undertaken. A most conservative estimate places the inoperability or questionable operability in the neighborhood of 50 per cent, or, in other words, this estimate comprises those patients who, by virtue of the extensiveness of the lesion, if not entirely inoperable, may be treated, at best, with a poor prognosis.

Tumors of the lateral and posterior walls and dome, by virtue of their situation, are most amenable to surgical excision and segmental resection, and in this situation these procedures offer the best prognosis.

Tumors of the Base of the Bladder.—Occlusion of one or both ureters by tumors of the base or their close proximity to the ureteral orifices and disposition of the ureters offer many obstacles to the successful treatment for tumors of the base of the bladder.

Lesions surrounding, obstructing, involving or encroaching on one or the other ureteral orifice, or those in which the ureters are encroached on in the removal of the lesion, require some disposition of the ureter in addition to eradication of the growth. Many such lesions may be hopefully removed by segmental resection, disposing of the ureter concerned by ligation or reimplantation into the bladder. My experience with these two methods of disposing of the ureter has been reported. Ascending infection presents the greatest hazard when reimplantation of the ureter is carried out, and in the series of cases at the Mayo Clinic previously reported the mortality for segmental resection and reimplantation of the ureter was 32 per cent as opposed to 13 + per cent for segmental resection and ligation of the ureter. Even though the kidney the ureter of which has been permanently ligated may need to be drained or removed subsequently an account of an infected hydro-nephrosis, such procedures were necessary in only 10 per cent of the cases in the series from the Mayo Clinic.

It would seem that the operation of cystectomy should have a wide field of application. However, this is not as yet the case, for in only a few instances are conditions such that cystectomy may be considered wise. Usually when the lesion is unsuitable for excision, resection, surgical diathermy or other physical agents, cystectomy is out of the question because of extravescical extension, remote metastasis, unilateral or bilateral partial or complete ureteral occlusion by the lesion or the poor condition of the patient. The magnitude of the operation of cystectomy with the simultaneous or preliminary disposition of the ureters is such that few patients with an extensive malignant growth of the bladder are suitable subjects for the procedure.

The disposition of the ureters has contributed greatly to the difficulties of the operation. Preliminary ureterostomy to the loin or inguinal area has facilitated subsequent cystectomy and has increased the safety of the operation, but presents the disadvantage of absence of a urinary receptacle. A number of cases have been reported in which the ureters have been transplanted into the sigmoid or rectum simultaneously with cystectomy, an operation that is accompanied by an extremely high mortality. The introduction of ureteral catheters into the ureters and bringing them out through the cystectomy wound or to the surface of the skin simultaneous with cystectomy has been a hazardous procedure because of ascending infection to the kidneys.

The perfection by C. H. Mayo and Coffey of methods of transplanting the ureters into the sigmoid has paved the way to the greater safety of cystectomy.

Beer recently reviewed the subject of cystectomy, presenting the advantages and disadvantages of the various methods of treating the ureters. Certainly the operative survival of seven patients whose cases were reported by him, from two months to as long as five years in one patient, represents an accomplishment which to my knowledge has not been equaled by any other method of cystectomy and simultaneous or previous disposition of the ureters.

DISCUSSION

JAMES EWING: This meeting demonstrates the importance of joint meetings between pathologists and clinicians. One might say that our clinical friends qualify for membership in the Pathological Society, first, at one extreme, owing to the great detail and accuracy with which clinical judgments have been based on thorough microscopic examinations, encouraging the pathologists to make these fine distinctions in the histologic study of tumors. And second, I think that the clinicians in this field deserve at least honorary membership in the society for having furnished us so much autopsy material from unexpected sources and so many tumors of the bladder under conditions in which we do not ordinarily obtain them. Our clinical friends might qualify as pathologists from both these points of view, and I wish that I could say as much for the pathologists. I do not think that pathologists are sufficiently acquainted with the clinical significance of some of the finer questions arising in the structure of tumors of the bladder to warrant being raised to the rank of genito-urinary surgeon. I trust that the demonstrations made here will encourage pathologists to learn more about the clinical aspects of the diseases with which they have to deal.

I was particularly interested in Dr. Aschner's classification and his minute discussion of the anatomic features, and I am in accord with his general point of view. He recognizes the simple benign papilloma as a strictly benign tumor. In another tumor, which is grossly a strictly papillary tumor, there are peculiar groups of atypical cells and in these he finds that the clinical history often indicates a malignant course, and therefore he calls this tumor a papillary carcinoma. I doubt if all papillomas showing these occasional groups of atypical cells run a malignant course, and I would prefer to class them as simple papilloma, while noting the increased possibility of recurrence associated with these atypical cell groups. Then he has a type of papillary tumor that is definitely atypical throughout, but not necessarily infiltrating the base, which he also calls a papillary carcinoma.

It seems to me that there is a marked difference between this group and the simple papilloma with atypical cell groups, and I would prefer to separate sharply between them, applying the term carcinoma only to the latter. Pathologists do not like to call a process "cancer" unless it shows definite histologic criteria of carcinoma, such as markedly atypical cells, loss of polarity and heterotopia, which signs are missing in the simple papilloma with scanty groups of atypical cells. Then he has others more advanced, malignant and atypical throughout and definitely infiltrating the stalk and the wall of the bladder, and he makes a separate classification of all of these. Finally, he has the flat carcinomas, which are generally infiltrating. I think that there is much practical advantage in making these distinctions, but whether there is any theoretical ground for separating them so minutely I am inclined to doubt. While I agree with Dr. Aschner that tumors starting at one tempo do not often become transformed into more malignant tumors, in a group of 100 tumors of the bladder you will find many stages between benign papilloma up to malignant carcinoma, and in the individual cases it is often difficult to apply these special terms satisfactorily. I do not think that it is wise to assume that carcinoma is something entirely different from a malignant papilloma. The two types of disease tend to run into one another, not that one case becomes transformed into the other, but that different cases cover all of the gradations between one class and the other. The attempt to emphasize great differences between a solid carcinoma and a malignant papilloma is therefore strained. Nevertheless, it is most significant that by this careful histologic analysis of tumors of the bladder, which I believe has been carried out more particularly in Mount Sinai Hospital than elsewhere, they have been able to show that the presence of these small groups of atypical cells in an otherwise benign papilloma carries with it an increased gravity in prognosis, and that is a significant thing for the pathologist. It encourages us to make more minute studies of histologic preparations, and to express opinions regarding the clinical course of the disease which we are as a rule loath to make, because the prediction of the clinical course of any tumor from the histologic section is always more or less hazardous. I do not know that there is any other field in tumor pathology in which such significance may be attached to the histologic structure. Possibly it is found in the larynx also. I have long since noted that the presence of a few atypical cells in a papilloma of the larynx generally signifies that the disease will recur and will kill the patient sooner or later. Pathologists may be encouraged to apply these criteria more carefully in other fields.

The question of histologic grading has long interested me. I am in favor of histologic grading carried as far as possible. While we have been grading tumors ever since the microscope has been used, the tendency to grade tumors more carefully has been increasing recently, owing to the work of Broders. I have little sympathy with the pathologists who, because of lack of knowledge or intellectual laziness, discard the matter of grading tumors as of no value and unsound. As industry increases and experience enlarges, most of these men will gradually see that they are finding an opportunity to serve the clinicians, which they should embrace under all circumstances. Therefore, I am in favor of the effort to grade tumors of the bladder, and we have had some satisfaction in our institution in this attempt. As I understand, Broders included in his group I of carcinomas of the bladder tumors that most pathologists call benign papilloma. His group II would probably fall in Dr. Aschner's class of papilloma with malignant cell groups. Therefore, we can readily understand why Broders' classes III and IV are the most numerous among the cancers of the bladder and are the malignant ones. We have found that there is considerable difference in the outcome of these four classes, but when it comes to making fine distinctions between groups III and IV, the true carcinomas, the clinical significance is perhaps not as great as it is in some other tumors, but it is still of value.

Another interesting point for the pathologist to keep in mind has been brought out by Dr. Hunt's remark that the malignancy of tumors in the bladder varies according to the location, the more malignant tumors being located in the trigone

and the less malignant ones at the fundus. This is also true of tumors of the alimentary tract, which increase in malignancy from the anus to the lips. These tumors vary in malignancy depending on location. In our head and neck service we are beginning to lay considerable stress on the location of a tumor, which in some instances seems to determine more or less the malignant course, even when it is of the same histologic structure as tumors located elsewhere which prove to be more benign. This again is a lesson which the clinician teaches the pathologist.

While the clinicians deserve membership in the Pathological Society because they have largely taken over the work of the pathologist, they have neglected some questions that are strictly clinical. I have not heard a word about the causation of cancers of the bladder. I have heard nothing about the importance of the age distribution in carcinoma of the bladder. I should like to know something about the general constitution of these patients and the previous history of the bladder. Has not the chemical analysis of the blood given some important information on this subject? If not, then it is the only subject in which it is not claimed to have made an important contribution. All of these questions belong in the realm of the clinician, and the clinicians seem to have left most of them for the pathologist to follow up.

EDWARD L. KEYES: I am not qualified to elucidate any further the differences in cellular malignancy. Although certain minor differences in opinion have appeared, we all agree on the important things, such as the use of the biopsy and the grading of tumors in one way or another. However, you will notice that there is great confusion in the fundamental use of the word malignancy. In both of the lists of statistics that have been shown, malignancy has been ultimately graded apparently in accord with the prospect of the death of the patient, as a result either of his tumor or of the treatment or lack of treatment. It is extremely difficult to disentangle these two items: the malignancy of the tumor itself and the malignancy of the surgeon who treats the tumor, or the lack of treatment that the tumor gets. Surely even a true carcinoma of the bladder may, if seen early enough, some times be controlled by relatively benign treatment. I have seen one such case, a primarily infiltrating tumor of the bladder, which I watched arise from beneath the mucosa and come through it, and that tumor has been controlled for several years, after the implantation of radium seeds through the cystoscope.

We should seriously push to the extreme limit in expert hands those methods of attack which are the least malignant. It is because of the lack of malignancy of the suprapubic operation for the implantation of radium that that method of approach has especially appealed to me. I will not quote statistics. In my hands the implantation of radium suprapubically has given me an operative mortality of less than 10 per cent. In other words, I have been less malignant than Dr. Hunt has. (I have perhaps been less efficient also. In certain individual cases it is impossible to compare results.)

I have been greatly interested in the use of diathermy, which again is a non-malignant method of treatment as compared to the radical methods which he, like other surgeons, used to employ. There is a general tendency, I think, on the part of the surgeons to become less malignant. I believe that it is along these lines that we shall progress, but we have a long way to go in weighing the advantage of cauterizing these tumors by the different physical agents, the electrocautery in contrast with radium. I favor the use of radium. I am not prepared to state that I have any facts to prove that my favoritism is justified.

BENJAMIN S. BARRINGER: You have heard both Dr. Aschner's and Dr. Hunt's careful and illuminating papers on the structure and surgical treatment of tumors of the bladder. I am personally much indebted to them for these papers. Rather than discuss Dr. Hunt's paper directly, I believe that it will fill out the picture to a certain extent to give the results of the treatment for cancers of the bladder by radium. Surgery and radium have long been contestants in the race for supremacy, and no one can say at present which will win. The comparison between results from radium and surgical treatment is difficult because surgery picks the

cases which are operable and discards the rest. At the Memorial Hospital we have subjected to irradiation every patient with cancer of the bladder in whom the cancer was believed to be confined to the bladder, no matter how large the tumor might be. Therefore, in our series are included many inoperable cases. Sixty-three and five-tenths per cent of the tumors involved were adjacent to the trigone, including in the growth one or both ureters or the internal urethral orifice. Twenty-eight per cent of the tumors had bases of 6 square centimeters (1 square inch) or less. In 72 per cent the bases of the tumor were greater than this, many of the tumors involving one half or one third of the wall of the bladder.

In the slides showing the result of radium implantation it is seen that the clinical diagnosis is often at variance with the anatomic diagnosis. This is unavoidable, as we have to be content with a small portion of the tumor for the histologic examination. Under these conditions the clinical diagnosis is more accurate than the microscopic diagnosis. For example, a microscopic diagnosis of a papilloma of a sloughing tumor has to be modified. A microscopic diagnosis of papillary carcinoma of a tumor the base of which is felt to be indurated and into which base a radium-bearing needle makes way as though going through gristle likewise has to be modified. This is an infiltrating carcinoma.

In this first group of slides I show sixty-two cases of carcinoma of the bladder that have been graded by Dr. Ewing and Dr. Stewart according to their malignancy and radiosensitivity. The diagnosis has been purely microscopic and not clinical.

The second group of slides shows the results of treatment in ninety-five cases, divided according to the older classification into papillary and infiltrating cancer. The diagnosis has been entirely from the microscopic side, leaving out of consideration the clinical diagnosis. The clinical diagnosis has at times been at variance with the microscopic diagnosis. No papillomas have been included in these series. They have been rigidly excluded. All of these tumors have been epithelial tumors.

The first series of slides consists of graded tumors. The number of cases is too small to be of much importance. The first is a papilloma with atypical cells, fourteen cases. We controlled eight cases, or 57 per cent, and the uncontrolled number was six, or 43 per cent. These are papilloma with atypical cells. The result of treatment shows that these tumors are real malignant tumors.

The second slide shows the papillary carcinoma, group I, 40 per cent of which were controlled, and 60 per cent uncontrolled.

The third is the papillary carcinoma, group II, of which 50 per cent were controlled and 50 per cent uncontrolled.

The fourth slide shows grade 3 of the papillary carcinoma, and while it is not shown in the classification, it has been of a great deal of interest to me that when we get to grade 3 the age of the patient begins to fall below 50, which of course should always be a clue in the history as to the possible gradation of the tumor concerned. In the more malignant cases, and here again the number of cases is too small to be of any real significance, the controlled cases comprise 37 and the uncontrolled 62 per cent.

The infiltrating carcinoma, group I, which includes four cases, shows a drop in the controlled cases, 25 per cent against 75 per cent uncontrolled. An interesting case is one that I have included several times in my control cases, and in which the patient lived for nine years and finally died of the infiltrating carcinoma.

The next group is infiltrating carcinoma, grade 2, comprising eleven cases; 27 per cent were controlled and 73 per cent uncontrolled.

The next group is infiltrating cancer, grade 3, comprising four cases; 50 per cent were controlled and 50 per cent uncontrolled. In this group of cases of grade 3 malignancy the ages begin to fall below 50, while in the other two groups there have been none below the age of 50.

I want to point to the value of classifying the tumors according to their malignancy. It enables a more accurate comparison of results. That is what we are all after. When we wish to compare our results, if we have graded tumors we

can more accurately compare them and know what each investigator is talking about. The grading determines the radiosensitivity of tumors, and therefore the proper dose of radium to be used. Radiosensitive tumors to be removed by operation or radium probably should be subjected to irradiation by deep therapy before the operation. The grading also gives some idea of the prognosis of a tumor.

The second set of slides shows the results of treatment in ninety-five cases, divided according to the older classification into papillary and infiltrating carcinoma. The diagnosis has been entirely from the microscopic side, leaving out of consideration the clinical diagnosis. There were fifty-one cases of papillary carcinoma; twenty-seven cases, or 52.9 per cent, were controlled; twenty-two cases, or 43 per cent, were controlled for more than three years, and 47.1 per cent were not controlled.

There were forty-four cases of infiltrating carcinoma; nineteen cases, or 43.1 per cent, were controlled; fourteen cases, or 31.8 per cent, were controlled for more than three years, and twenty-five cases, or 56.9 per cent, were not controlled.

The third set of slides shows the results from radium in 125 cases in which the diagnosis was from the clinical side. This diagnosis has at times been at variance with the microscopic diagnosis. There were forty-five cases of papillary cancer; thirty cases, or 66 per cent, were controlled and twenty-five cases, or 55.5 per cent, were controlled for more than three years. Of eighty-two cases of infiltrating cancer, thirty, or 36.5 per cent, were controlled; twenty-three, or 27.8 per cent, were controlled for more than three years, and fifty-two, or 63.5 per cent, were not controlled.

Finally, I shall stress the decided difference between the operative mortality when a tumor is removed by surgical procedures and when it is implanted by radium. In 108 consecutive cases of suprapubic implantation of radium, four patients died in the hospital, an operative mortality of 3.7 per cent. This includes all cases, small and large, in which the tumor was thought to be confined to the bladder. In 62 per cent of these cases the tumor touched some part of the trigone, the ureters or the internal urethral orifice. In those cases in which the tumor could have been removed surgically, and there were many in which it could not, the operative mortality would have been from 15 to 20 per cent in the most competent hands.

PAUL W. ASCHNER: I hoped that I had made myself clear. I do not like the term "malignant papilloma," and I did not use it. It did not appear in any of the tables, and it was mentioned only as one of the great sources of confusion. We diagnose cases as papilloma, as papillary carcinoma, noninfiltrating, as papillary carcinoma, infiltrating and as nonpapillary or flat carcinomas. When the pathologist reports a biopsy specimen as grade I in Broders' terminology, he certainly takes a great load off his own shoulders, because this grade of tumors includes both the cases which we recognize as benign papillomas, and some of those which Dr. Ewing and I recognize as definitely malignant tumors.

Dr. Barringer's interesting tables will no doubt prove of much value. However, I wish to point out that the diagnosis of infiltrating carcinoma is not purely a microscopic diagnosis. It is also a gross or a clinical diagnosis. The papillary carcinoma may or may not infiltrate. The flat carcinoma usually infiltrates.

The things that I want to stress are the accuracy of the biopsy in arriving at a diagnosis of malignancy, our inability to draw conclusions as to prognosis from biopsy alone and our belief that cytology alone is insufficient for grading tumors. I feel sure that when Dr. Ewing grades his tumors he is not guided by cytology alone. Certainly the clinician feels that the location of the growth and the extent of infiltration are of equal or greater importance in prognosis.

VERNE C. HUNT: I again want to repeat what I said in closing, that cancer of the bladder is still a very serious disease. I think that there is room for improvement in the results, and I think that the only way that such improvement will occur is through a comparison of the results obtained in definitely graded lesions, graded microscopically, and through a comparison of the results obtained

by the various therapeutic methods that are employed—surgical intervention, the various physical agents and what not—which calls to my mind again what Dr. Keyes and I were talking about this noon. He recently sent out letters to the effect that all tumors of the bladder be examined in various clinics and be sent into the registry to be gone over, so that a definite classification of the tumors of the bladder may be accepted, if such a thing is possible. First of all, before we can obtain accurate results and compare the relative merit of the various therapeutic agents used, the surgeon, the pathologist and the clinician must talk the same language. That can be accomplished only through the registry that has been formulated, so that these tumors are examined at a certain place and by certain men and some degree of agreement is arrived at.

I had hoped that there would be some discussion regarding the structure of these lesions. You have heard about papillary carcinomas and infiltrating carcinomas, and I have been talking about epitheliomas. The reason I talked about them is because I talked with Dr. Broders at the Mayo Clinic before I came here. I called him up and said, "You have told me this before, and as I have gone over the records I find that the tumors of the bladder are epitheliomas. Is it true that 95 per cent of the bladder tumors are epitheliomas?" He said, "They are." Other pathologists look at them as carcinomas. We must get together so that we all talk the same language. When that is accomplished, we can then begin to determine the relative merit of various physical agents, surgical procedures and so on, and not until then. I think that only through the comparison of methods can we learn. The future is open. I think that we are making progress.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, March 13, 1930

BALDUIN LUCKÉ, *President, in the Chair*

FIBROMYOMA OF UTERUS WEIGHING ONE HUNDRED AND THIRTY-THREE POUNDS REMOVED AT OPERATION. MOSES BEHREND.

Mrs. A. P., aged 35, was admitted to Mount Sinai Hospital, on March 3, 1930. She said that nine years previously she was seized with sharp abdominal pain in conjunction with her menstrual period. About that time she noticed a small swelling in the lower part of the abdomen which had become progressively larger up to the time of presentation. She had walked and had worked as a druggist up to six weeks before presentation. She complained of thirst and dyspnea, but no urinary symptoms, and the bowels were regular. Menstruation began at 13, was always regular and was not painful. She had menstruated about three times in the past three years. Notwithstanding the size of the tumor, she said that she enjoyed good health, with the exception of weakness for the last six weeks. She had never been pregnant.

The abdomen was greatly enlarged, measuring 5 feet 8 inches (172.7 cm.) in circumference. The skin over the abdomen and the legs were edematous. Hard masses were felt on the lateral sides of the abdomen, with soft areas here and there. The mass was painless. On March 3, a tumor weighing 133 pounds (60.3 Kg.) was removed.

A GIANT CELL TUMOR WITH METASTASES OCCURRING IN A CHACMA BABOON, PAPIO PORCARIUS. HERBERT L. RATCLIFFE.

A case of giant cell tumor occurring in a Chacma baboon is described. The growth originated near the lower epiphysis of the ulna, perforated the shaft and articular cartilage and infiltrated surrounding tissue. The development was rapid,

the tumor being discovered about three months before the animal was killed. At autopsy, metastases were found in the lungs, heart and gluteus muscles. An attempt to transplant this tumor to two rhesus monkeys failed.

MENINGOCOCCUS MENINGITIS ASSOCIATED WITH A GRAM-NEGATIVE BACILLUS.
A. I. RUBENSTONE and I. DAVIDSOHN.

A girl, aged 12, was admitted to Mount Sinai Hospital in August, 1929, with clinical signs and symptoms of meningitis. The spinal fluid contained 1,450 cells, with 95 per cent polymorphonuclears. The direct smears of the spinal fluid showed gram-negative bacilli and diplococci, mostly intracellular. The diplococci proved culturally to be meningococci. The bacilli were motile organisms which stained characteristically darker at the ends. They produced acid and gas in dextrose, mannite, xylose, maltose, levulose, rhamnose and blackened lead acetate. They did not ferment lactose, saccharose, raffinose, salicin, arabinose, dextrin, dulcitol and inositol. Indol was not produced. Gelatin was not liquefied. In Russel's medium, the slant was alkaline and the butt acid, with a slight formation of gas. The milk was not coagulated. The reaction was slightly acid during the first forty-eight hours, then it became alkaline and remained so during the observation time of fourteen days. The organism was so placed in the group of *Salmonella*, but it differed slightly from any known member of that group. Cultivation on the synthetic mediums of Pesch and Kortenhaus did not help to identify the organism. Also agglutinations, absorptions and cross-agglutination tests did not place the organism in a definite subgroup of *Salmonella*. It probably belongs to one of the irregular members of that group.

The same organism could not be found in any other part of the patient's body. The patient's serum agglutinated it completely in a dilution of 1:30 and partly in a dilution of 1:50, while normal control serum produced only a partial agglutination in a dilution of 1:4. From the finding of the organism intracellularly in the direct smears jointly with a meningococcus and from the agglutination reaction with the patient's own serum, it is concluded that a mixed infection of the meninges was present. The patient was treated with antimeningococcus serum; she recovered within thirty days.

CHANGES IN THE SKIN REACTION TO HISTAMINE OCCURRING IN THE COMMON PERIPHERAL VASCULAR DISEASES. ISAAC STARR, JR.

The changes in the skin reaction to histamine have been studied in the common peripheral vascular diseases. The reactions above the knee or the wrist were always normal; those distally varied as follows: In diabetic arteriosclerosis (100 cases) the observations permit the classification of the patients as follows: Group 1: Pulsation in the peripheral arteries obliterated, histamine reaction delayed and incomplete. This is interpreted as indicating obliterative arterial disease without collateral compensation. Group 2: Peripheral pulsation obliterated, reaction normal; suggesting obliterative arterial disease with complete compensation by collateral circulation. Group 3: Peripheral pulsation present, histamine reaction delayed and incomplete; suggesting a pathologic condition in the smaller arteries. The frequent absence of flaring in the presence of whealing in this group demonstrates the great frequency of peripheral neuritis in diabetes. If gangrene is present in the feet, all reactions below the knee are usually abnormal.

In advanced nondiabetic arteriosclerosis (thirty cases), the reactions of the skin of the feet to histamine are usually incomplete or delayed unless hypertension is present. If the blood pressure of a patient who shows normal reactions when hypertensive falls to a normal level, the histamine reactions become delayed or incomplete, returning to normal as the blood pressure rises to its previous level. These observations demonstrate the importance of hypertension in compensating for sclerotic changes in the arteries.

In Buerger's disease (five cases) the reactions are normal down to a certain level, below which they become markedly retarded or incomplete. This level is

located on the distal part of the foot in early cases; it is higher in later ones. The flares are well preserved, often being present when whealing is absent.

In embolism of an arm or leg (three cases), the reactions gradually become more abnormal as one goes distally from the location of the embolus. There is no sharp line of change at the level of the embolus.

In Raynaud's disease (five cases), the reactions to histamine vary with the conditions of the vessels, being incomplete during periods of arterial spasm and normal when spasm is absent.

In achrocyanosis (two cases with redness but no pain), the flares in the involved area are higher and appear more promptly than in normal persons. The wheals are normal.

In one case of scleroderma of the hands, the reactions on the involved skin were normal. In a second case complicated by advanced peripheral arteriosclerosis, the reactions were normal on the involved skin of the face, trunk and proximal parts of the limbs, but became progressively more abnormal distal to the elbows and knees.

EXPERIMENTAL HYPERSENSITIVENESS TO DERIVATIVES OF PNEUMOCOCCUS. LOUIS A. JULIANELLE.

From this series of studies concerning the reactions of rabbits to injections of pneumococci and their products, it appears that when heat-killed pneumococci or their products are repeatedly injected into rabbits, intravenously or intracutaneously, the rabbits become hypersensitive to subsequent intracutaneous injections of pneumococcus proteins, as shown by a reaction in the skin, which is analogous to the phenomenon of Arthus as exemplified in rabbits following injections of nonbacterial protein. The development of this hypersensitiveness occurs simultaneously with the development of species-specific antibodies in the blood, and this type of hypersensitiveness may be transferred to normal rabbits following the transfer of blood serum from the sensitive animals. The development of this type of sensitivity seems to bear no relation to active immunity, since animals repeatedly given injections of soluble products of the pneumococcus cells show no active immunity, but nevertheless are skin reactive.

When the whole, killed bacteria are repeatedly injected intracutaneously, another type of hypersensitiveness, in addition to that just described, makes its appearance. This is shown by the fact that animals treated in this way react in a different manner to the individual injections of the bacteria into the skin. At the first injection a reaction occurs in the skin, a primary reaction, which disappears after a few days, but is followed in about ten days by a recrudescence. This recrudescence occurs even without a second injection, and is probably an evidence of the development of hypersensitiveness.

With repeated intracutaneous injections of the whole organisms, the skin reaction gradually becomes more severe; secondary reactions occur, however, only after the first injection. After from four to six injections have been made into the skin, the reactions become of lessened severity and are also modified in character. During the course of injections, therefore, the skin reactions are probably different from unmodified Arthus reactions, although the Arthus type of sensitivity is coincidentally present in the animals, as is shown by their exhibition of typical Arthus reactions when they are given injections of small amounts of pneumococcus protein twenty days later. That another type of sensitivity develops in these animals is also shown by the fact that they become eye sensitive to pneumococcus protein, while animals treated in other ways never do. Apparently, when bacteria are localized in the skin, a new and different kind of hypersensitiveness develops.

The reactivity manifested by the eye was found to be unrelated to type-specificity or to the formation of circulating antibodies. Unlike the reactivity of the skin to pneumococcus protein, the reactivity of the eye is not transferred to normal rabbits following the transfer of blood from sensitive to normal animals. While the skin reactivity occurs in resistant and nonresistant rabbits, the eye reactivity has been observed only in animals resistant to infection.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

CARL V. WELLER, *Secretary**University of Chicago, March 27, 28 and 29, 1930*WILLIAM F. PETERSEN, *President*

BACTERIOLOGIC AND SEROLOGIC OBSERVATIONS IN BRUCELLA ABORTUS INFECTIONS. M. H. SOULE, UNIVERSITY OF MICHIGAN.

These studies were undertaken to evaluate the presence of blood serum agglutinins and blood stream infection in relation to milk agglutinins and milk infection. The tests were made on more than 5,000 ordinary herd-run cows used for the production of milk. The animals were distributed as follows: 2,032 in Wisconsin, 1,736 in New York and 1,664 in Michigan. Two series of tests were made on each animal at intervals of approximately six months. The blood serums were tested for agglutinin content in dilutions of 1:50, 1:100, 1:200, 1:300 and 1:500, against living suspensions of *Brucella abortus*, strain 80. The blood was cultivated for *Brucella abortus* by the addition of 50 cc. samples of blood to 450 cc. volumes of sterile glycerol infusion broth and subsequent incubation in air enriched with carbon dioxide. The blood was diluted as soon as withdrawn and was not chemically treated or defibrinated to prevent clotting. At two to four day intervals, samples were removed and streaked on the surface of glycerol infusion agar. No blood samples were considered negative previous to six weeks' incubation. The presence of agglutinins in the milk was detected by taking 20 cc. samples from each quarter of the udder, treating them with rennet and then using the clear milk serum, in the dilutions given, for the blood serum tests. *Brucella abortus* was isolated from the infected milk by the injection of 5 cc. samples of milk from each quarter of the udder into the peritoneal cavity of guinea-pigs. At the end of five weeks the guinea-pigs were killed. If the spleens showed enlargement with tubercle-like lesions they were cultured on glycerol infusion agar, in air plus carbon dioxide. In the first series of tests agglutinins were present in the blood stream of 2,237 of the animals, but only 299 gave positive blood cultures. In the second series of tests agglutinins were present in 2,607 cases with 206 positive blood cultures. There were 40 positive blood cultures without concomitant blood agglutinins. The milk samples showed a greater parallelism between agglutinin content and milk infection. In the first tests 1,219 milk serums contained agglutinins with 1,143 positive cultures for *Brucella abortus*. The second series gave 1,544 positive agglutinin tests and 1,367 positive cultures. There were no positive cultures in samples free from agglutinins. There were 156 positive milk cultures in the first tests without parallel blood agglutinins, and in the second series there were 194 positive milk cultures without accompanying blood agglutinins. These results indicate that the presence of agglutinins for *Brucella abortus* in the milk is a better index of milk infection than the presence of blood stream antibodies. The data obtained in the three states were uniform, indicating the widespread distribution of these organisms.

THE MECHANISM OF ANTIBODY ACTION IN RELATION TO PHAGOCYTOSIS AND OTHER SURFACE PHENOMENA. MORTON McCUTCHEON, BALDUIN LUCKÉ, STUART MUDD AND MAX M. STRUMIA (BY INVITATION), UNIVERSITY OF PENNSYLVANIA.

We have previously reported that whenever acid-fast bacteria were prepared by serum for phagocytosis certain definite changes in the surface properties of the bacteria could be demonstrated. The surface changes correlated with increased phagocytosis are increased cohesion, decreased surface electric potential difference and decreased wettability by oil.

As the result of these studies we were led to the hypothesis that each of the several reactions is determined by the coating of the particle with some serum constituent or constituents. In the present investigation we have obtained evidence

that this constituent is associated with the globulin fraction. Acid-fast bacteria, coated with globulin which has been precipitated from immune serum and then resuspended, behave essentially like those treated with whole immune serum as regards both phagocytosis and other surface reactions. With serum albumin, similar effects were not produced.

The next step was to determine whether globulin plays an equally important rôle in immunity reactions when antigens other than acid-fast bacteria are used. Rabbits were immunized against soluble antigens: egg albumin, human serum, casein and edestin. Colloidion particles coated with one of these antigens were exposed to the corresponding immune serum and its fractions. The results were in every way similar to our previous ones: Particles coated with globulin were prepared for phagocytosis, were agglutinated and had cohesiveness increased and electric charge reduced. We believe, therefore, that these several reactions brought about by specific immune serums depend on the coating of the particle by some substance or substances present in the globulin fraction.

THE HYDROGEN ION CONCENTRATION OF THE INTESTINE. J. L. BOLLMAN AND F. C. MANN, MAYO FOUNDATION.

A method has been devised whereby small samples of intestinal contents may be removed at frequent intervals from any portion of the intestine without noticeable disturbance to the animal. Permanent intestinal fistulas were prepared in the following manner. A loop of terminal ileum, about 10 cm. in length, was isolated and the continuity of the intestine maintained by end-to-end anastomosis. The distal end of the isolated loop was then anastomosed end-to-side to the desired portion of the gastro-intestinal tract, and the proximal end of the isolated loop was brought through the abdominal wall and sutured to the skin. In a short time complete healing occurred and the animals appeared entirely normal. Samples of intestinal contents were obtained at frequent intervals during the course of digestion of various meals. The hydrogen ion concentration was determined with the quinhydrone gold electrode system immediately after withdrawal of the samples.

The observations in the first portions of the small intestine showed the greatest changes. In the fasting dog the duodenal contents were usually found to be about p_H 7.6 with occasional variations (in the same animal), seldom as low as p_H 6.2. When milk was fed it began to appear in the duodenum within a few minutes, but there was only a slight diminution of the p_H in the first thirty minutes. After this time, rapid fluctuations in p_H occurred, most determinations being in the region of p_H 5.5, with frequent values of p_H 4.6 and occasional readings of p_H 6.6. About two hours after milk feeding the p_H was more constant and began to rise to about 6.8. Normal fasting values were obtained shortly after this period but wide variations in time occurred; in some animals fasting values were not obtained for twelve hours after feeding, but usually about five hours were required. Following meat feeding the course of events was similar to that described for milk except that the p_H tended to be slightly lower.

The p_H values in the jejunum, 50 cm. from the ligament of Treitz, were more constant. The fasting level varied from p_H 7 to 7.6 and was somewhat influenced by the previous diet. Milk feeding decreased the p_H to about 6.8 for about four hours after feeding, and rapid fluctuations did not occur. After meat feeding the p_H sometimes fell to 6.2 for this same period.

In the ileum, 100 cm. from the ligament of Treitz, changes in the p_H due to digestive processes were not apparent. The fasting p_H was from 7.2 to 7.8 and was somewhat influenced by the previous diet. Occasionally after meat feeding the p_H decreased to 7.

THE INCUBATION PERIOD IN PASSIVE SENSITIZATION WITH HOMOLOGOUS ANTISERUM. JULIAN H. LEWIS, THE OTTO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE UNIVERSITY OF CHICAGO.

The fact that a definite latent period is necessary before the appearance of anaphylactic sensitization after the injection of an immune serum is regarded as

important evidence in support of the cellular theory of anaphylaxis. This latent period is believed to be utilized in fixation of antibodies by the body cells concerned in the anaphylactic reaction and would not be necessary if anaphylactic shock were the result of an interaction of antigen and antibody in the circulating blood as is assumed in the humoral theory of anaphylaxis. Friedberger questioned the necessity of an incubation period in passive anaphylaxis; he claimed that the appearance of an immediate sensitization is prevented as the result of using a foreign sensitizing serum since foreign serums inhibit anaphylactic shock, not only after passive, but also after active sensitization. If the use of a foreign serum is avoided by using an homologous sensitizing serum no inhibition occurs and therefore no incubation period is necessary. Friedberger stated that guinea-pigs sensitized with intravenous injections of guinea-pig immune serum give severe and fatal anaphylactic reactions from three to five minutes after the injection of the sensitizing serum.

The poor response which guinea-pigs give to attempts to produce precipitating serum and the high mortality associated with intensive methods of immunization make it difficult to repeat the experiments of Friedberger. Seibert showed that tuberculous guinea-pigs and those immunized by repeated injections of tuberculin protein have surprisingly high titers of precipitins for the tuberculin protein, reaching in some instances 1:1,000,000. Lewis and Seibert further showed that such serums, in keeping with other precipitating serums, are very active in passively sensitizing guinea-pigs. The ease with which these serums are produced makes possible a thorough testing of Friedberger's observations.

The pooled serum from sixteen guinea-pigs with antituberculin precipitating titers ranging from 1:1,000 to 1:50,000 was titrated for passive sensitizing power. The minimal fatally sensitizing dose given intravenously and with an incubation period of twenty-four hours was 1 cc. A series of guinea-pigs received injections of 2 cc. of this serum into the jugular vein, and after periods ranging from three to ten minutes the proper dose of antigen was injected into the opposite jugular vein. These remained entirely unaffected. Another series was sensitized in the same way and received intravenous injections of antigen at various intervals ranging from two to eighteen hours. After two hours there was no reaction, fatal sensitization first appearing four hours after sensitization. As the uterus strip technic is a more sensitive test for anaphylaxis, it was used in virgin female guinea-pigs one, two, three and four hours after an injection of 2 cc. of the sensitizing serum. A positive reaction first appeared at the end of two hours, reaching its maximum at the end of four hours. Since it is possible to maintain an isolated uterus strip in an active condition for two hours it was thought possible to sensitize this tissue *in vitro* by exposing it to antiserum for this length of time. A normal uterus suspended in an oxygenated warm bath of Tyrode solution containing 2 cc. of anti-tuberculin guinea-pigs' serum (a dilution of 1:250) gave a markedly positive reaction at the end of two hours.

Friedberger's claim, therefore, that an anaphylactic reaction can be obtained without an incubation period when passive sensitization is produced with homologous antiserum, is not corroborated.

THE NATURE OF THE IMMUNITY OF THE SKIN OF THE GUINEA-PIG TO STAPHYLOCOCCUS INFECTION. G. A. PACHECO AND PAUL R. CANNON, THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE UNIVERSITY OF CHICAGO.

A histologic study of the skin and subcutaneous tissues of the abdominal wall of normal guinea-pigs and of those previously immunized by intracutaneous injections of a staphylococcus vaccine, all infected by the intracutaneous injection of a live virulent culture of *Staphylococcus aureus*, revealed the following general facts: The inflammatory response in the normal animals is characterized mainly by an infiltration of polymorphonuclear leukocytes in moderate numbers, with the result that the infection disseminates and becomes an extensive cellulitis in many instances. In the previously immunized animals, however, the response is more energetic, the exudate contains a large proportion of mononuclear cells and there is increased

activity of the tissue macrophages in the subreticular layer. In addition, immunization leads to a marked thickening of the entire skin, due mainly to increased numbers of fixed tissue phagocytes being either activated or produced, or both. Because of the hyperergic response of the tissue macrophages and of mobile elements as well, the infection is circumscribed and terminated. The conclusions drawn are that the immunity resulting from the intracutaneous vaccination with dead staphylococci is a cellular immunity due to stimulation of the reticulo-endothelial elements of the subcutis, which are not only increased but also react more quickly in phagocytizing and digesting the living staphylococci later injected.

THE EFFECT OF MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS ON THE ANTI-COAGULANT ACTION OF WITTE'S PEPTONE. ELIZABETH CRANSTON (BY INVITATION), O. R. CAILLET (BY INVITATION) AND J. P. SIMONDS, NORTH-WESTERN UNIVERSITY.

It was shown in previous experiments that mechanical obstruction of the hepatic veins is accompanied by a marked reduction in the coagulation time of the blood. Witte's peptone in suitable doses decreases or completely inhibits the coagulation of the blood. When peptone is injected intravenously during mechanical constriction of the hepatic veins, (1) there is a delay in the appearance of its anticoagulant action and (2) its anticoagulant effect is less marked. Peptone is believed to reduce the coagulability of the blood through its effect on the liver. Mechanically shutting the liver out of the circulation, however, does not completely prevent this action of peptone.

EFFECTS OF CHOLECYSTECTOMY ON THE BILIARY SYSTEM. CLAIRE HEALEY, ALLAN G. REWBIDGE AND BÉLA HALPERT, INTRODUCED BY H. GIDEON WELLS, THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE UNIVERSITY OF CHICAGO.

Opinions differ regarding the effects of the surgical removal of the gallbladder on the rest of the biliary system. In order to gather first-hand information, a preliminary study was made on twelve dogs. The condition of the biliary system was noted at operation; gross and microscopic examination of the gallbladder was made, and the rest of the biliary system was similarly studied after removal from two to sixteen weeks following cholecystectomy. The results thus far obtained suggest the following conclusions: 1. The effects of cholecystectomy depend primarily on the preoperative working condition of the biliary system and on individual anatomic variations regarding the arrangement of the ducts. 2. Cholecystectomy is not followed by dilatation of the intrahepatic biliary ducts. 3. The dilatation of the extrahepatic biliary ducts, if it occurs, is independent of the time elapsing after removal of the gallbladder.

PLASMA p_H IN CANCER. FRITZ BISCHOFF, M. LOUISA LONG (BY INVITATION) AND ELSIE HILL (BY INVITATION), SANTA BARBARA COTTAGE HOSPITAL.

The plasma p_H of fifteen normal persons, fifteen patients with cancer who had received no treatment, and ten patients with cancer who had taken radium, x-ray or lead treatment was determined directly by means of the quinhydrone electrode at room temperature. The results were corrected with the oral temperature of the subject for comparison. The normal group showed an average plasma p_H of 7.46 with a minimum value of 7.43 and a maximum value of 7.50. The patients with cancer who had received no treatment showed an average p_H of 7.50, with a minimum value of 7.44 and a maximum value of 7.59. Two thirds of the values for this group were above the highest value obtained in the normal group. The patients with cancer who were under treatment showed an average p_H of 7.52. The observations do not agree with those of Millet who reported no difference between his patients who were normal and those who had cancer.

BLOOD CHEMISTRY STUDIES WITH HENS BEARING ROUS SARCOMA NO. 1. JOSEPH H. ROE, GEORGE WASHINGTON UNIVERSITY.

Chemical analysis of the bloods of hens bearing Rous sarcoma no. 1 showed no variations from control values in nonprotein nitrogen, uric acid, creatinine, chlorides, cholesterol, serum calcium and inorganic phosphorus, hemoglobin and bilirubin, the analyses being performed at times varying from eighteen days before death to the day of death. A distinct elevation of the blood sugar level was noted. Studies of the blood enzymes showed no variation from control values for the glycogenolytic enzymes of the blood of the sarcoma-bearing hens; but the glycolytic activity of the sarcoma-bearing hens was found to be about twice as great as that of control hens.

THE EFFECT OF SUPRARENAL CORTICAL SUBSTANCE ON THE OVARIES OF CHICKENS AND ON CHICKEN TUMORS. CHARLES L. CONNOR, UNIVERSITY OF CALIFORNIA.

An emulsion of suprarenal cortex in Ringer's solution, freed as far as possible of epinephrine and excess protein, constantly causes degeneration and atrophy of the ovaries of laying hens when injected subcutaneously or intravenously. The hens stop laying almost immediately, and in many of them aborted eggs are found free in the peritoneal cavity. Eggs and follicles which remain attached to the ovary undergo cystic or hemorrhagic degeneration. When the substance is injected into chickens that have not reached the age of puberty, the ovaries cease growing. A few crowing cocks were injected; in these the testes seemed smaller than in controls and spermatogenesis was absent. The effect seems to be the same as that caused by adrenal cortical tumors in man in whom an excess secretion causes a neutralization of the sex glands.

Because of the known, or suspected, effect of the ovaries on certain tumors in man, chickens that had been inoculated with Rous sarcoma were treated with this substance. It produced contradictory results, as some of the treated animals died before the controls, some died at about the same time, and a few lived longer than might be expected without some sort of treatment.

THE EFFECT OF MUSCULAR WORK ON THE CALORIGENIC ACTION OF THYROXIN. C. M. WILHELMJ (BY INVITATION), O. B. BUCKLEY (BY INVITATION) AND W. M. BOOTHBY, THE MAYO CLINIC.

The calorogenic action of a single intravenous injection of 10 mg. of thyroxin, in the same dog, when maintained under the same conditions of nutrition, environment, etc., has been previously shown to be constant. In the present series of experiments we studied the influence of daily muscular work of mild, moderate or severe nature on the curve of extra heat production following the injection of 10 mg. of thyroxin. The basal metabolism was determined each morning following the injection of thyroxin, and during the afternoon the animal was given various degrees of muscular work on a motor driven treadmill. In control experiments on the same animal the basal metabolism was likewise determined each morning following the administration of the thyroxin, but during the afternoon the animal was allowed to rest in a small individual metabolism cage under which condition muscular movements were at a minimum. The results show clearly that the extra heat production which follows the injection of thyroxin, in the dog, is not reduced by muscular work; in fact there is a suggestion that the extra heat production may be greater than when the animal is allowed to rest. These observations suggest that muscular work does not increase the rate at which thyroxin is destroyed or eliminated from the body.

THE EFFECT OF SAPOTOXIN AND SODIUM TAUROCHOLATE ON NERVOUS TISSUE. ARTHUR WEIL, NORTHWESTERN UNIVERSITY, INTRODUCED BY J. P. SIMONDS.

In a previous report it was demonstrated that hemolytic toxins, like saponin, cobra venom, streptolysin and sodium taurocholate, act destructively on the myelin sheaths of nerve fibers. Furthermore, it was found that the myelolytic action of

these toxins as well as their toxic effect on rats could be inhibited in the same way as hemolysis by the addition of cholesterol, lecithin, suspensions of red blood cells, brain emulsions, etc. The possible relationship of these phenomena to certain neurologic diseases with primary demyelination was discussed.

In order to overcome the objection that different components of these toxins might produce different biologic action, sapotoxin was isolated from Quillaja saponin in the form of a chemically pure substance. It could be demonstrated that it had the same biologic effects as saponin but was more potent, while the residue of saponin after the elimination of sapotoxin was without effect. According to E. St. Faust, the active principle of cobra venom is closely related to sapotoxin. With sodium taurocholate different histologic pictures are obtained than with sapotoxin. The latter dissolves the myelin sheaths, while the former breaks them up into fine globules which stain dark black with myelin sheath stains. The histologic pictures of cobra venom and streptolysin demyelination resemble that of sapotoxin.

THE LEUKOCYTE CURVE AND ORGAN REACTIONS. E. F. MÜLLER (BY INVITATION) AND W. F. PETERSEN, UNIVERSITY OF ILLINOIS.

The fluctuations of the peripheral leukocyte count, when followed at short intervals over a long period of time, afford an index of the autonomic status of the peripheral tissues, distribution leukopenia being associated with lessened tissue activity, and leukocytosis with increased activity. Many factors may influence this status. Charts were presented to illustrate some of them. Frequently the waves are of increasing amplitude following a single insult. Leukocytic reaction of the internal organs and the possible mechanism of the fluctuation were discussed.

ALTERATION IN THE RESPONSE TO INSULIN DURING EXPERIMENTAL LEUKOCYTOSIS. ISOLDE T. ZECKWER, UNIVERSITY OF PENNSYLVANIA.

Each of eight rabbits, under standard conditions, was injected on several occasions with a small convulsive dose of insulin. Then an intense leukocytosis was induced by the intravenous injection of 0.1 Gm. of sodium nucleinate. In five rabbits during the period of leukocytosis, about eighteen hours after injection of the nucleinate, the previously convulsive dose of insulin no longer induced convulsions. These rabbits were allowed to return to normal conditions, when the same dose again caused convulsions. On again inducing leukocytosis by nucleinate, convulsions were again inhibited.

It was necessary to determine if the inhibition of insulin action was due to the leukocytosis or to some other effect of sodium nucleinate. When sodium nucleinate is injected repeatedly, the bone-marrow becomes exhausted of its myeloid elements, so that a rise in circulating leukocytes no longer occurs. When rabbits which previously had shown insulin inhibition during leukocytosis were brought to the stage where sodium nucleinate no longer caused leukocytosis, convulsions again occurred when the same dose of insulin was given, as though no nucleinate had been injected. This would appear to indicate that inhibition of insulin action had occurred because of leukocytosis. The blood sugar just before the insulin was injected was within the normal range in the rabbits so far described.

In three rabbits no inhibition of insulin action occurred during nucleinate leukocytosis, but in these rabbits the blood sugar was low just before the injection of insulin, about eighteen hours after the injection of the nucleinate.

It was found that in the intact rabbit, sodium nucleinate injected intravenously caused an abrupt rise in blood sugar, with a maximum amount at about one hour, followed by a fall to normal or slightly below. The rise did not occur if, some time previous to the injection, one adrenal gland was excised and the opposite splanchnic nerve cut. It was found that insulin inhibition could be induced during nucleinate leukocytosis in two rabbits in which glycogenolysis was prevented by excising one adrenal gland and cutting the opposite splanchnic nerve, if the blood sugar level was within the normal range at the time of the injection of insulin. It was concluded

that when inhibition of insulin action occurred, it was dependent on leukocytosis, not on any effect of nucleinate in mobilizing glycogen.

Since insulin is inactivated in vitro by the enzymes of leukocytes, it is considered that the insulin inhibition during leukocytosis is probably dependent on the enzymes of the circulating leukocytes. No definite conclusions can be made until more data are obtained, until it is ascertained whether absence of convulsions can be taken as a criterion for inactivation of insulin, and until it is possible to explain those cases in which convulsions were not inhibited during leukocytosis.

CONSECUTIVE BLOOD COUNTS ON NORMAL RABBITS OVER LONG PERIODS OF TIME. LOUISE PEARCE AND ALBERT E. CASEY (BY INVITATION), THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.

Consecutive blood counts on groups of normal rabbits have been carried out over long periods of time for the purpose of obtaining information on the character of the spontaneous variations in the numbers of erythrocytes and of leukocytes and in the hemoglobin content. The observation periods were eight, thirteen, twenty-six, twenty-nine, and thirty-five weeks, respectively; the animal groups comprised four of ten rabbits each and one of five rabbits; the rabbits were young adult males from approximately 6 to 8 months of age, of the common brown or gray type and were representative of those used in other experiments in this laboratory. The examinations were made at weekly intervals, and the supravital neutral red technic was used for the differential white cell counts. The mean values of each weekly group of observations were used in analyzing the results which have been considered primarily from the standpoint of the general trends of cell levels.

It was found that the mean group values of the cells and the hemoglobin content showed certain definite major trends which were of statistical significance. In the first year, both the red cells and the hemoglobin levels became increased; in the second, the red cells were maintained at a fairly constant level but the hemoglobin was increased. In both years, the values for the total white cell count, the neutrophils and the lymphocytes were augmented. The basophils were increased during the first, but were diminished during the second, year. The most prominent feature of the eosinophil results was the abrupt appearance and the comparatively short duration of large numbers of these cells in the peripheral blood, which occurred principally in the spring months. The monocytes showed increased values in the fall and spring months, but on the whole, no generally sustained upward trend of mean values, as was the case with the lymphocytes and neutrophils. The greatest irregularity in the mean values of the various white cells and of the hemoglobin content occurred during the late winter and spring months of both years. The results in the groups examined during 1927-1928 differed from those examined in 1928-1929 in that the general level of mean values of the various cells and of the hemoglobin content tended to be higher during the first year. It was found also that two groups of rabbits examined during the same months usually showed similar and, on the whole, coincident changes in the major trends and even in the more minor fluctuations of mean values.

The value to be attached to these observations is twofold. First, the results furnish information on the character of the spontaneous variations of certain blood constituents which ultimately may be found to have some relationship to environmental conditions. Second, in experimental disease conditions of a subacute or chronic nature, as for example in *Treponema pallidum* infections, the significance of any hemocytologic variation must be interpreted with due regard to the changes that have been demonstrated in normal rabbits over correspondingly long periods of time.

DEVELOPMENT OF THE MYELOBLAST IN CHRONIC MYELOGENOUS LEUKEMIA. RAPHAEL ISAACS, UNIVERSITY OF MICHIGAN.

The chromosome number in developing myeloblasts in chronic myelogenous leukemia was 24 in the material studied, in comparison with the usual somatic

number of 48. It is suggested that the reduction in number may have represented an accident in cell division with viable daughter cells which had abnormal growth properties and defective ability to mature. The reduction is similar numerically to that taking place in the developing germ cells, and the clinical results of roentgen therapy in leukemia may be analogous to the artificial parthenogenesis induced in unfertilized germ cells by these agents.

EXPERIMENTAL STUDIES ON MOUSE LEUKEMIA. MAURICE N. RICHTER AND E. C. MACDOWELL, COLUMBIA UNIVERSITY, INTRODUCED BY A. M. PAPPENHEIMER.

In a previous communication we recorded the existence of a strain of mice in which lymphatic leukemia occurs with great frequency, and reported the successful transmission of leukemia to normal young mice of the same strain. In subsequent experiments it was found that the disease may be transmitted by inoculation of emulsions of various tissues (spleen, liver, lymph node, blood) and that further transfers are possible, apparently indefinitely. In some of the experiments positive results have followed the use of tissues for subsequent transmissions within twenty-four hours after inoculation, but when emulsions prepared from such tissues are used, a longer time is required for the development of leukemia than when the inoculum is prepared from tissues of more advanced cases. The agent responsible for the transmission of leukemia is unknown. Thus far, our experiments indicate that the living cell, or an agent inseparable therefrom is necessary.

Differential counts of living and dead cells in the emulsion (trypan blue method) at the time of inoculation, and experiments with diluted emulsions, indicate that the efficacy of the material, as judged by the time required to cause death from leukemia, is correlated with the number of living cells inoculated. Procedures that deleteriously affect the viability of the cells, such as subjection to heat, or grinding with sand or glass, cause a prolongation of the period of survival which is, roughly, of the same order of magnitude as the increase in the number of dead cells.

Emulsions in which all the cells are killed (by heat, glycerin, or desiccation) or from which the cells have been removed (by filtration or centrifugalization) have been ineffective.

EXPERIMENTAL PRODUCTION OF AN ALEUKEMIC LEUKEMIC CONDITION (A PRELIMINARY REPORT). BERNHARD STEINBERG, TOLEDO, OHIO.

An organism with many of the characteristics of *Bacillus proteus* was isolated from the bone-marrow of a boy, aged 15. The patient had marked anemia, leukopenia and a relative lymphocytosis. All the viscera showed a marked lymphoid infiltration. This micro-organism was introduced into the bone-marrow of rabbits, with a reduplication of the blood picture and some of the visceral changes observed in the patient. The organism was recovered in pure culture from the marrow of other bones in the animals given injections. Intravenous and intraperitoneal injections of the bacillus failed to reproduce the disease. Introduction of other micro-organisms—*Staphylococcus aureus* and a hemolytic streptococcus—failed to duplicate the pathologic picture obtained with the bone-marrow organism. The bone-marrow of the patient and of the experimental animals revealed an erythroblastic as well as a mononuclear and lymphoid cell hyperplasia. The total pathologic picture of the patient and of the rabbits was that of so-called aleukemic leukemia.

THE BEHAVIOR OF CERTAIN VITAL DYES INTRODUCED INTO THE CIRCULATION. H. P. SMITH, UNIVERSITY OF ROCHESTER.

A study was made of the fate of certain acid vital dyes when introduced into the circulation of dogs. These dyes were taken up and stored in granular form in certain phagocytic cells. Evidence showed that the dye is distributed between

plasma and cells in definite ratios. Any disturbance in this equilibrium is followed by passage of dye to or from the cells, with the result that a new equilibrium is established.

THE EFFECT OF FEEDING ON THE RATE OF REMOVAL OF INTRAVENOUSLY INJECTED PRODIGIOSUS BACILLI FROM THE BLOOD STREAM OF DOGS. J. C. RHEINGOLD, UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F. PETERSEN.

Bacillus prodigiosus, injected intravenously, disappears at a more rapid rate from the blood stream of fed than of starved dogs. The mechanism of the removal of the organisms is essentially agglutination followed by filtration in the capillary bed (of the splanchnic organs particularly) and their ultimate fate is destruction by the reticulo-endothelial cells. The mechanisms of the increased reticulo-endothelial activity are discussed.

ALKALOSIS OBSERVED IN CASES WITH PERSISTENT HYPERTENSION. EDWARD MUNTWYLER AND C. T. WAY, WESTERN RESERVE UNIVERSITY, INTRODUCED BY V. C. MYERS.

An acid-base equilibrium study of the plasma has been made on cases with persistent hypertension and with only slight nitrogen retention. A report of three cases is made, and at the present time a study is being conducted of two more cases showing similar results. If one assumes 31 mm. as the upper limit for a normal bicarbonate concentration, there was in each case a condition of alkalosis at some period in the observation. The first case showed an uncompensated alkalosis over a period of twenty-two days just preceding death, with the p_H varying between 7.54 and 7.56 and the bicarbonate between 34.2 and 36.6 mm. In the second case, which did not present as severe an alkalosis as the first, 34.5 mm. was the highest observed bicarbonate concentration. Both cases were characterized by a progressive fall of chloride and total base with a greater decrease of the former than of the latter. Since both of these cases showed periodic vomiting, this may have been the paramount factor in producing the bicarbonate excess, though this cannot be accepted as final as no analyses of the vomitus were made. The third case differed from the first two in that there was no progressive decrease of the chloride and total base concentrations, and further, vomiting was not present. In spite of a normal concentration of chloride there was a bicarbonate concentration of from 28.3 to 32.2 mm. existing over a period of four months. From that time on there was a progressive decrease in bicarbonate to give a terminal uncompensated acidosis. Since the total base in this case remained normal, the undetermined acid concentration (phosphates, sulphates and organic acids) showed a progressive increase.

EXPERIMENTAL PRODUCTION OF INSULIN NEPHROSIS. MILTON G. BOHRD, UNIVERSITY OF ILLINOIS, INTRODUCED BY H. R. JAFFÉ.

Normal and pancreatectomized dogs were given large doses of insulin. If the latter lived for more than twenty-four hours, swollen, anemic kidneys were found which were the seat of vacuolar degeneration. Normal dogs died, too, soon after the administration of insulin and revealed similar changes. The condition produced is considered to be an insulin nephrosis, probably due to a disturbance of the water metabolism.

EXPERIMENTAL CANINE DIABETES INSIPIDUS. S. J. MADDOCK, PETER BENT BRIGHAM HOSPITAL, INTRODUCED BY HARVEY CUSHING.

A series of dogs was studied in which diabetes insipidus was produced by closing a silver clip on the stalk of the hypophysis. In one of these animals the polyuria persisted for eighteen months. A complete report of the clinical and

pathologic observations in this dog is presented, together with a brief discussion of the rôle played by the nerve tracts in the tuber cinereum in this syndrome.

INTRARENAL ARTERIAL TUBERCULIN INJECTIONS IN NORMAL AND TUBERCULOUS MONKEYS, GOATS AND SWINE. ESMOND R. LONG, CHARLES B. HUGGINS AND ARTHUR J. VORWALD, UNIVERSITY OF CHICAGO, INTRODUCED BY H. GIDEON WELLS.

A previous report showed that renal inflammatory changes can be induced by tuberculin injected into the renal arteries of tuberculous swine. In the present report the response in swine and other animals is compared. Tuberculous *Macacus rhesus* monkeys proved to have low sensitiveness to tuberculin. Skin tests led to a soft superficial edema, with little inflammatory change. In two out of three tuberculous monkeys, renal arterial injection of a fine suspension of coagulated tuberculin protein caused a tubular degeneration with many hyaline and waxy casts, but no glomerular or intertubular inflammatory changes, as shown by biopsy a few days after the operation. Autopsy from one to two months later showed complete recovery. Tuberculous goats proved highly skin-sensitive to tuberculin. Of three tuberculous goats one suffered slight tubular degenerative changes on the renal arterial injection of tuberculin protein, one showed acute degenerative changes on the second of two injections, with slight inflammation, and the third showed acute tubular degeneration in the first kidney, injected with many hyaline and waxy casts. A subsequent injection of tuberculin protein into this kidney three months later led to the production of an enormous number of hyaline and waxy casts with no appreciable inflammation and little apparent tubular degeneration. Tuberculous swine were only moderately skin-sensitive to tuberculin. Renal arterial injection in all of three tuberculous swine caused profound fatty degenerative changes in the tubular epithelium, with hyaline and leukocytic casts. In one of these there was marked, and in another moderate, interstitial infiltration with cells of inflammation. Glomerular changes were lacking in all three swine. Biopsy or autopsy a month later showed almost complete recovery. A second renal arterial injection, in the opposite kidney, led abruptly to death in each of two animals so treated. In all animals of each series focal lesions were found which were obviously the result of thrombosis or embolism of small vessels. Two control animals of each type treated in the same manner as the tuberculous animals showed no other changes than those attributed to this focal vascular damage.

THE TEMPERATURE AND ASSOCIATED SERUM CHANGES IN TUBERCULOSIS. KNUTE REUTER, UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F. PETERSEN.

By means of blood samples taken at frequent intervals during twenty-four hour periods, an effort was made to correlate the alterations in the serum of tuberculous patients with the temperature reaction. Fluctuations of the peripheral leukocyte count, the sugar curve and the enzyme reaction (crepsin) revealed definite relations to the clinical observations.

A QUINHYDRONE-COLLODION ELECTRODE OF SPECIAL APPLICABILITY IN EXPERIMENTAL PATHOLOGY. JOHN C. BUGHER, UNIVERSITY OF MICHIGAN, INTRODUCED BY CARL V. WELLER.

A small portion of the fluid to be examined is isolated by the use of a collodion membrane and the contained fluid saturated with quinhydrone. The potential difference developed between a gold-plated platinum wire contained within the small collodion sac and a reference half-cell connected to the outside fluid by a saturated potassium chloride bridge is a function of the hydrogen ion activity of the fluid. The membrane potential is negligible when electrolytes are present in a concentration of one-tenth molar or more. Quinone and hydroquinone, into which quinhydrone dissociates, diffuse through the membrane at practically equal rates, so

that their original ratio is unchanged. The salt effect of the electrode is the same as in other uses of quinhydrone. The electrode is stable in all biologic fluids, including whole blood. It may be incorporated with an electrode vessel forming part of a closed system so that the partial pressures of the contained gases may be maintained at their desired values.

The curve representing the approach to equilibrium is transcendental in character and the equation may be derived directly from the law of diffusion of a solute through a homogeneous phase. The rate at which a given electrode approaches its equilibrium value depends on the thickness of the quinhydrone deposit and on that of the membrane, and is independent of the size of the platinum wire.

The construction of this electrode was illustrated and described.

INFLUENCE OF CLIMATE AND DIET ON GASTRO-INTESTINAL DISEASES. LLOYD ARNOLD, UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F. PETERSEN.

The seasonal variation of the incidence of gastro-intestinal diseases was approached from an experimental angle. There is normally a natural protective mechanism against infection by the oral ingestion of bacteria causing enteric diseases. This bacteria-destroying power is found to be located in the upper half of the small intestine. When an animal is in a state of physiologic equilibrium this segment of the small intestine is almost sterile, and foreign bacteria ingested by mouth or placed directly within the lumen of the upper levels of the enteric tract are destroyed. Body changes brought about by summer temperature, diet and other environmental alterations cause a demonstrable change in the self-disinfecting power of the upper half of the small intestine. Not only do bacteria survive within the lumen, but there is some evidence that permeability of the tract is increased.

This represents a study of the physiologic changes in the host that increase the significance of the microbic life in and around the host.

THE ABSORPTION OF ULTRAVIOLET LIGHT BY BACTERIA. FREDERICK L. GATES, THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH AND HARVARD UNIVERSITY.

In the ultraviolet region between 220 and 300 millimicrons, different bacteria such as *Staphylococcus aureus* and *Bacillus coli* show characteristic absorption bands so similar as to indicate that they are due to identical chemical groups in the two organisms. Among the chemical entities derived from protoplasm, two groups give absorption bands similar to those for the intact cell. It is evident that one or both of these groups are present in sufficient concentration in the bacterial bodies to dominate in ultraviolet absorption and so to determine their characteristic curves. One of these groups is that of the aromatic amino-acids, built on the benzene ring. The other is made up of certain nuclear derivatives built on the pyrimidine ring. Further study may disclose a means of distinguishing between these two groups in ultraviolet absorption, and of determining which one is primarily involved in such a reaction, for example, the bactericidal action of ultraviolet light, the incident energy curve for which is approximately reciprocal to the absorption curve for the bacteria in the same region.

THE STRAIGHT AND DIFFUSE PENETRATION OF ULTRAVIOLET LIGHT INTO THE HUMAN SKIN. A. BACHEM (BY INVITATION) AND C. I. REED, UNIVERSITY OF ILLINOIS.

By use of various methods, the penetration of visible light and ultraviolet rays, from 576 to 236 millimicrons, through various specimens of human skin was determined. The various sources of error were studied or analyzed carefully, and special care was used to imitate the treatment conditions by diverging the experiments. It could be shown that the penetration is governed more by scattering than by

true absorption. The distribution of the light through the various layers of skin was determined and the practical limit established that the various parts of the spectrum reach.

THE EFFECT OF IRRADIATION BY THE MERCURY VAPOR ARC ON THE ACTIVITY OF PEPSIN AND TRYPSIN. DEB B. CALVIN, UNIVERSITY OF MISSOURI, INTRODUCED BY A. GULICK.

THE EFFECTS OF SOLAR IRRADIATION OF LONG VISIBLE AND ULTRAVIOLET WAVELENGTHS RESPECTIVELY, WITH AND WITHOUT SUPPLEMENTARY IRRADIATION OF VARIOUS TYPES, ON THE GROWTH OF CHICKS AND THE DEVELOPMENT OF PARATHYROID GLANDS. CHARLES SHEARD, GEORGE M. HIGGINS (BY INVITATION) AND WILLIAM I. FOSTER (BY INVITATION), THE MAYO FOUNDATION.

Under the experimental conditions employed, the grade of stock used and the ration fed in our investigations we believe:

1. Constant housing of chicks behind an amber glass filter which transmits only the longer visible wavelengths of sunlight definitely retards growth and development and allows hyperplasia, cystic degeneration and fibrous invasion of the parathyroid glands to occur.

2. Constant housing of chicks behind a filter (red-purple corex) which transmits practically only the ultraviolet region 270-400 millimicrons, with a maximal transmission of 20 per cent at 330 millimicrons, rarely permits normalcy in development and growth of chicks as evidenced by weight, and it induces hyperplasia, cystic degeneration and fibrous invasion of the parathyroid glands.

3. Normal weights and normal development of parathyroid glands are found in chicks constantly housed behind an amber filter and given daily supplementary irradiation from ten to fifteen minutes with an air-cooled quartz mercury lamp operated at 90 volts and at a distance of 50 cm. (ultraviolet irradiation of approximately 575 ergs each second for each square millimeter).

4. Normal calcification of bones (as evidenced microscopically by the Becke method and by the percentage of calcium by weight) and normal weights of chicks occur under several of the experimental conditions imposed relative to quality and quantity of energy with, however, the presence of abnormal parathyroid glands. The absence of evidences of rickets or of malnutrition does not argue, therefore, for normalcy of parathyroid glands.

5. Further evidence is presented, therefore, to support our statement that normal growth and development of chicks and of the parathyroid glands are dependent on both the ultraviolet and the visible portions of solar irradiation, all other factors remaining constant so far as is known.

SULPHYDRYL AS A STIMULANT TO CELL DIVISION IN MAMMALS. STANLEY P. REIMANN, THE LANKENAU HOSPITAL RESEARCH INSTITUTE.

Hammett has shown that the sulphydryl group is essential for cell division and that without it, cell proliferation cannot occur. The present communication shows that the -SH group attached to such organic radicles as dextrose and cresol increases the rate of cell division in rats and human beings. In rats, areas of skin of equal size were removed from each side of the back; dextrose was applied to one side and thiiodextrose to the other. The wounds to which thiiodextrose was applied healed much more rapidly than the others, or normal wounds in these animals.

In human subjects the application of thio-compounds also stimulated healing in such conditions as chronic leg ulcers and bed sores. Therefore it was concluded that the group -SH, since it also stimulates division in mammals, is a universal stimulant to mitosis.

THE RELATION OF INJURY TO PERMEABILITY OF THE CELL TO WATER. BALDUIN LUCKÉ AND MORTON MCCUTCHEON, UNIVERSITY OF PENNSYLVANIA.

The unfertilized egg of the sea urchin is an excellent natural osmometer that permits both recognition of injury by decisive criteria and precise measurement of permeability. It has previously been shown that the course of osmosis is satisfactorily described by certain equations by which permeability may be expressed in terms having a definite physical meaning, viz., the number of cubic microns of water entering or leaving the cell per minute, per square micron of cell surface, per atmosphere of difference in osmotic pressure between the interior of the cell and the external medium.

In the present experiments the injurious factors employed were heat and anisotonic solutions. The results were:

1. Cells injured by heat (from two to four minutes' exposure to 44 C.) remained capable of swelling and shrinking in anisotonic solution.

2. The cells swelled rapidly in hypotonic solutions for a period of several minutes after which they shrank, whereas normal cells continued to swell until equilibrium was attained.

3. When permeability at the first minute was determined in cells exposed to a temperature of 39 C. for two, four, eight, twelve and sixteen minutes, and subsequently caused to swell in hypotonic sea-water, a regular series of values was obtained, unheated (control) cells having the lowest permeability and those heated for sixteen minutes the highest.

4. When cells heated for four minutes at 31.0, 36.5, 39.0 and 41.5 C. were caused to swell in hypotonic sea-water, the values of permeability were found to vary directly with the temperature.

5. After exposure to a higher temperature (45 C.), or prolonged exposure (sixteen minutes) to 44 C., cells were incapable of swelling in hypotonic solutions.

6. When previously normal cells were caused to swell in different hypotonic solutions the values of permeability were the same when calculated for successive minutes (at least during the first several minutes). Increased permeability was found to be an expression of injury.

7. When normal cells previously swollen in hypotonic solutions were returned to isotonic solution and allowed to shrink, the value of permeability was found to be approximately identical for the cells from the different hypotonic solutions. Injured cells, however, had a higher permeability.

8. It was concluded that injury does not at once nor completely destroy the semipermeability of the cell, and that the permeability of injured cells to water is greater than that of normal cells.

AN ACTIVATED EXTRACT FOR COAGULATING HEPARIN PLASMA. JOSEPH T. KING, UNIVERSITY OF MINNESOTA, INTRODUCED BY F. H. SCOTT.

At present, heparin plasma is widely used in routine planting of tissue cultures. The plasma is coagulated by the addition of an extract of some tissue, usually embryonic tissue.

It has been found possible to increase greatly the power of chick extract to coagulate heparin plasma (rabbit) by adding a small amount of plasma to the extract. After a frail clot has formed, the small amount of fibrin is removed. The extract now is found to have a higher coagulating value. Further, it retains its power over a longer period of time.

The amount of plasma required is small. One part to from 60 to 100 parts extract is used as a routine.

This more powerful extract permits the use of higher concentrations of heparin; spontaneous coagulation of the plasma in storage is thereby avoided and the operator is assured of prompt clotting when planting.

ALLERGIC, ANAPHYLACTIC AND IMMUNE REACTIONS FOLLOWING INOCULATION OF GUINEA-PIGS WITH HEAT KILLED TUBERCLE BACILLI (READ BY TITLE). ARNOLD BRANCH AND J. R. CUFF (BY INVITATION), HARVARD MEDICAL SCHOOL.

The term allergy is employed here to mean that a necrotic reaction occurred after the intracutaneous inoculation of 0.1 cc. or 5 per cent old tuberculin, that Long's intratesticular tuberculin reaction was elicited, and that Pfeiffer's intraperitoneal reaction was present. The term anaphylaxis is used when typical lethal or nonlethal shock occurred after the intravenous inoculation of 0.5 cc. of old tuberculin. Immunity was considered present when a lymphocytic rather than a monocytic reaction occurs in animals reinfected in the peritoneum or pleura, and when animals inoculated with small doses of living virulent tubercle bacilli outlive controls and show less tuberculosis at death. "Late tuberculin death" signifies that the animals died within twenty-four hours, with subnormal temperature, following a subcutaneous inoculation of 0.5 cc. of old tuberculin.

The intraperitoneal, intrapleural or intratesticular inoculation of from 3 to 5 mg., dry weight, of heat-killed (100 C. for one-half hour) tubercle bacilli (H 37) in 1 cc. of saline solution resulted in allergy, relative immunity and anaphylaxis. Anaphylaxis usually appeared in three weeks and lasted about two months. Allergy usually appeared before anaphylaxis and lasted a longer period. On the other hand, a like dosage of organisms in like dilution, inoculated in two sides intramuscularly, produced anaphylaxis and relative immunity but no allergic reaction. Large doses sometimes produced allergy. Intravenously inoculated animals also showed no allergy, but immunity was not well marked. Late tuberculin death was not elicited in animals inoculated with heat-killed organisms, but in the doses used skin hypersensitivity was not demonstrable in dilutions of old tuberculin above 1:1,000. In infected animals, no matter whether the lesions were localized or disseminated, allergy was readily elicited but anaphylaxis rarely. Skin reactions were often positive to a 1:100,000 dilution of old tuberculin. Late tuberculin death was elicited in all infected animals with one exception, and this animal gave a positive reaction only to a 1:1,000 dilution. The immunity of infected animals was not tested.

Histologic examination of lesions following the various methods of inoculation of heat killed organisms revealed that caseation was always present in allergic animals and absent in nonallergic ones.

These experiments suggest that tuberculous allergy and anaphylaxis are different phenomena, that immunity may occur without allergy and that late tuberculin death occurs only in infected animals that are highly sensitive to intracutaneous inoculation. This is probably a purely quantitative phenomenon, although other possibilities have not been entirely excluded.

Book Reviews

THE PRINCIPLES OF BACTERIOLOGY AND IMMUNITY. By W. W. C. TOPLEY, M.D., Professor of Bacteriology and Immunology, University of London, Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine; and G. S. WILSON, M.D., Reader in Bacteriology and Immunology in the University of London, London School of Hygiene and Tropical Medicine. Price, \$15. Pp. 1300, in two volumes, with 242 figures. New York: William Wood & Company, 1929.

This noteworthy book is designed primarily for the student seeking a more thorough training in bacteriology than that offered by the current medical, veterinary or public health curriculum. It is based on the experience of the authors in elementary and advanced teaching and follows the course of study in the London School of Hygiene and Tropical Medicine, with the omission, however, of detailed technical descriptions. There are four parts: general bacteriology, systematic bacteriology, infection and resistance and the application of bacteriology in medicine and hygiene. The first two parts form the first volume; the last two, the second. The pages of the text, the chapters and the figures are numbered consecutively from one volume to the other; both volumes have the same title, but each has its own index and there is no general index. It is, in fact, one book with the index for the first half in the middle. Of course, this is awkward. Even if an index of the first volume seemed desirable, an index covering the whole work at the end of the second volume would have been logical and practical. But this blunder can be remedied easily in the next edition, which surely will be forthcoming before long. The book reflects good standards of workmanship—the page is pleasing, the print clear, the binding substantial and the illustrations, simple as they are in black and white, instructive and helpful.

One may say without qualification that the book is a successful attempt to present adequately the state of knowledge and the trends of advance in the various parts of the broad field of bacteriology and immunity as it relates to infection. The accounts are clear and well balanced; the historical basis in the main is secure; conflicting views are stated with obvious fairness; there is no obscurity in presentation, no undue simplification and no hesitation in stating that no definite conclusion can be drawn from the available evidence when such appears to be the case, as happens to be true frequently (see especially the chapters on hypersensitiveness and on herd infection and herd immunity). At the end of each chapter is a list of references cited in the text which will guide the student in further reading. Naturally many questions might be raised and discussed, for instance: Is the use of the American nomenclature of bacteria, as modified by the authors, warranted? Several surprises, some of them perhaps annoying, await readers especially interested in this question, but the authors are not arbitrary in such matters and always advance reasons that command serious consideration. To some it will seem that the discussion of toxins and antitoxic immunity fails to reach adequate clearness and precision because the use of the word toxin is not limited as exactly as may seem justified from the point of view of the immunologist. Fortunately this is one of few books to give a satisfactory account of the work on the events associated with the formation, course and significance of antibodies in the animal organism. A curious lapse is the complete failure to take any notice of the recent work on the toxigenic action of erysipelas streptococci. While the main purpose of the book is to educate the student to an understanding of bacteriology and its problems, scientific as well as practical, its value as a source of reference and an account of summaries of recent advances should not be overlooked. The student who masters the principles of the book at the same time as he receives commensurate practical training builds a safe foundation for future work.

THE *PENICILLIA*. By CHARLES THOM, Principal Mycologist, Bureau of Chemistry and Soils, United States Department of Agriculture; assisted by Margaret B. Church, O. E. May and M. A. Raines. Price, \$10. Pp. 644, with 99 illustrations. Baltimore: William & Wilkins Company, 1930.

The first paragraph of the introduction gives a good idea of the subject of this book: "The molds of the genus *Penicillium* share with the *Aspergilli* and the *Mucors* a noisome preeminence as weeds. They rot our fruit, attack our vegetables and meats, injure our stored grain, spoil our soft drinks and our bottled water, contaminate our pantries and kitchens, and even attack our bodies. They infect and at times destroy the usefulness of solutions and moist precipitates, discolor fibers, wood, paper stock, stored paper and sometimes our books. In the laboratory they infest and often invalidate every kind of culture operation, bacteriological, mycological, or phanerogamic. To offset these activities the chemists have gathered a little return by using them in biochemical investigations and the cheese industry has capitalized their enzymic activity to ripen such cheeses as Camembert and Roquefort. Otherwise their possibilities of usefulness remain mostly unknown, but their presence is thrust upon us so frequently that some means of identifying them is very desirable."

The author has been working on the classification of *Penicillia* since 1904, and presents a complete and authoritative work on their history, description, classification and industrial and pathogenic significance, with keys to the identification, bibliography and species, as well as a general index. The chapter on pathogenic *Penicillia* is by Margaret B. Church and summarizes the recorded reports, most of which are fragmentary and inconclusive. The collection of molds of the American Type Culture Collection, with headquarters at the John McCormick Institute for Infectious Diseases, Chicago, is maintained in the Bureau of Plant Industry of the United States Department of Agriculture at Washington, and in it will be found type forms of *Penicillia* described by Thom or received as exchanges. This book and the book on *Aspergilli* by Thom and Church (Williams & Wilkins Company, 1926) are great landmarks in the study of molds to which all students of molds must turn for guidance.

A MANUAL OF EXTERNAL PARASITES. By HENRY ELLSWORTH EWING, United States Bureau of Entomology. Price, \$4.50 (by mail, \$4.66). 96 illustrations. Springfield, Ill.: Charles C. Thomas, 1929.

The main object of this book is to furnish brief sketches of the principal morphologic characters of the external parasites, their life histories and their natural relationships. The parasites in question are the mites, the ticks, the biting lice, the sucking lice and the fleas. This includes the rat flea concerned in the transmission of plague; the itch mite; the ticks of Rocky Mountain spotted fever, of Texas fever, and of spirochetosis of fowls; the sucking lice of relapsing fever, of trench fever and of typhus fever. In preparing the keys for identification, the large collection of parasites recently given to the National Museum by Dr. E. A. Chapin was found of great help. This collection is in the charge of the author. There is an abundance of good black and white illustrations, and the book contains a large amount of detailed and exact information clearly set forth, with valuable suggestions for control and protection.

Books Received

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE. Ein Handbuch und Lehrbuch für Morphologen, Physiologen, Praktische Ärzte und Studierende. Unter Mitwirkung Zahlreicher Fachgenossen, Begründet von Weil. Prof. Dr. Ernest Schwalbe Herausgegeben von Dr. Georg B. Gruber, o. ö. Professor der Pathologie an der Universität Göttingen. III Teil: Die Einzelmissbildungen XIV. Lieferung 3. Abteilung 5-7. Die Entwicklungsstörungen der Hyphophyse von Prof. Dr. E. J. Kraus; Missbildungen der Nebennieren von Dr. W. Pagel, Sommerfeld-Osthavelland. Die Missbildungen der Epiphyse des Gehirns von Dr. H. Wurm, Heidelberg. Price, 6 marks. Pp. 574, with illustrations. Jena, Germany: Gustav Fischer, 1929.

THE LIFE OF HERMANN M. BIGGS, M.D., D.Sc., LL.D., PHYSICIAN AND STATESMAN OF THE PUBLIC HEALTH. By C. E. A. Winslow, Dr.P.H., Professor of Public Health, Yale School of Medicine; Member, Health Committee, League of Nations, Geneva; Member, Public Health Council, State of Connecticut; Past President, Society of American Bacteriologists and American Public Health Association. Cloth. Price, \$5 net. Octavo, pp. 432, with illustrations. Philadelphia: Lea & Febiger, 1929.

THE CHEMICAL ASPECTS OF IMMUNITY. By H. Gideon Wells, Ph.D., M.D., Professor of Pathology, University of Chicago; Director of Medical Research, The Otho S. A. Sprague Memorial Institute. Second edition, revised and enlarged. American Chemical Society Monograph Series. Pp. 286. New York: The Chemical Catalog Company, 1929.

DIE FRAGE NACH DEM URSPRUNG DER ENDOMETRIOIDEN HETEROTOPIEN BEIM GESCHLECHTSREIFEN WEIBE. Von Dr. Konrad Heim, Privatdozent für Geburtshilfe und Gynäkologie, Oberarzt an der Klinik. Price, 8 marks. Pp. 110. Berlin: S. Karger, 1929.

DIET AND THE TEETH: AN EXPERIMENTAL STUDY: I. DENTAL STRUCTURE IN DOGS. By May Mellanby. Medical Research Council, Special Report Series no. 140. Price, 17 shillings, 6 pence. Pp. 308, with 109 plates. London: His Majesty's Stationery Office, 1929.

A CLASSIFICATION OF BRIGHT'S DISEASE. By Dorothy S. Russell. Medical Research Council, Special Report Series, no. 142. Price, 8 shillings, 6 pence, paper. Pp. 248, with 16 plates. London: His Majesty's Stationery Office, 1929.

THE PENICILLIA. By Charles Thom, Principal Mycologist, Bureau of Chemistry and Soils, U. S. Department of Agriculture, assisted by Margaret B. Church, O. E. May and M. A. Raines. Price, \$10. Pp. 644, with 99 illustrations. Baltimore: Williams & Wilkins Company, 1930.

RADIUM IN GENERAL PRACTICE. By A. James Larkin, B.S., M.D., D.N.B., Radium Consultant on Staffs of Wesley Memorial, German Evangelical Deaconess, John B. Murphy and Washington Park Community Hospitals, Chicago, and St. Francis Hospital, Evanston, Ill.; Instructor in Dermatology (Radium), Northwestern University Medical College. Price, \$6. Pp. 304, with 28 illustrations. New York: Paul B. Hoeber, Inc., 1929.

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